NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

For committee – contains AIC information

Pre-meeting briefing

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

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Key issues for consideration
Clinical effectiveness

- What is routinely used to treat articular cartilage defects in the NHS?
- Are all the relevant comparators included in the submission?
  - Company does not include traditional autologous chondrocyte implantation (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 pooled analysis
  - Are the studies adequately similar to be pooled?
  - Are the estimates from the pooled analysis valid?
- Is chondrosphere a clinically effective treatment?
  - For any lesion size?

Key issues for consideration
Cost effectiveness

- Are the modelled treatment pathway and treatment sequences appropriate?
- 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?
- Equalities issues

Chondrosphere
(Spherox, co.don)

MARKETING AUTHORISATION
"adults with symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV), single or several adjacent lesions with a combined area of up to 10cm^2"

Composition and mechanism of action

Spheroids (tiny pearl of cartilage cells and material) of human autologous matrix-associated chondrocytes for implantation suspended in isotonic sodium chloride solution

To make spheroids, a small healthy cartilage sample is taken from the joint of the patient in an operation and grown in the laboratory over 6-8 weeks. The spheroids are applied evenly into the defected cartilage area and stick to the defect site with no need for fibrin glue or cover flap. The spheroids repair the defect with healthy and functional cartilage over time

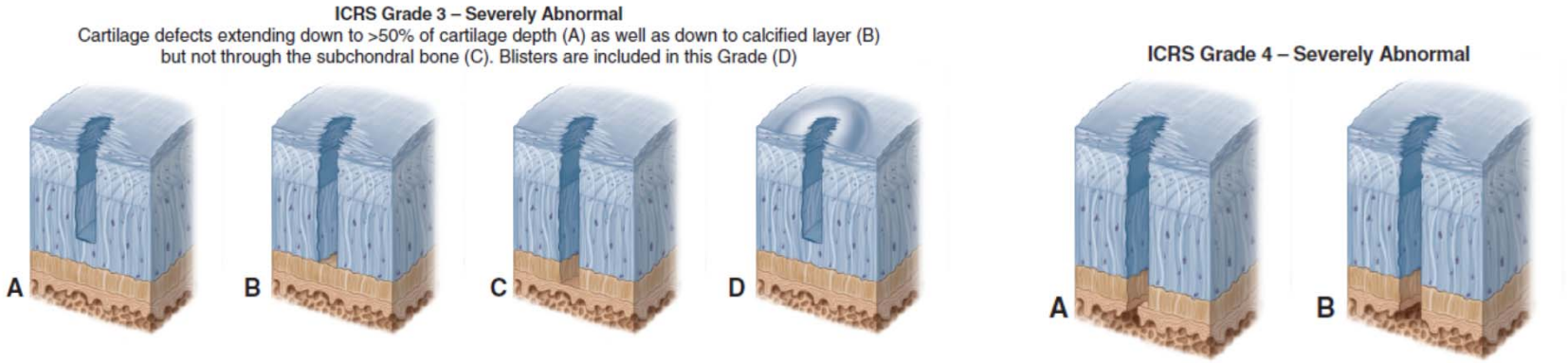
Administration and dose

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
- Precursor to long-term musculoskeletal morbidity
- Mechanism of injury: injury, wear and tear, knee instability, abnormal unbalanced pressures, obesity leading to excessive weight bearing

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 cells are seeded to a membrane or “scaffold” Technology: MACI® Vericel (not currently licensed)	
Generation: 4th Does not need flap, membrane or scaffold Technology: Spherox (currently licensed)	Current appraisal

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

Decision problem

ERG: company submission specifically focuses on adults with cartilage defects of the knee; intervention and outcomes are the same as the NICE scope

Population	**NICE scope:** people with articular cartilage defects **Company submission:** adults with articular cartilage defects of the knee

	NICE scope and Company submission
Intervention	chondrosphere
Outcomes	• pain • joint function including long-term function • rates of retreatment • activity levels • avoidance of osteoarthritis including joint replacement • adverse effects of treatment • health-related quality of life

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 (subject to ongoing NICE appraisal) [now published as TA477, ACI recommended] • Knee debridement • Mosaicplasty • Best supportive care (non-operative intervention)	**Include** • Microfracture – company's market research suggest most widely used in NHS • Autologous chondrocyte implantation – ChondroCelect and VeriMACI only **Exclude** • Traditional ACI – only available at 1 centre in England, under hospital exemption on a non-routine basis • Knee debridement – used before or after ACI or microfracture • Mosaicplasty – used in about 7% of knee lesions in the NHS 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

Key outcome measures (1)

Primary outcome: knee injury and osteoarthritis score (KOOS)

Knee Injury and Osteoarthritis Score (KOOS) – Primary outcome

- 5 subscales (questions relate to previous week): pain (9), symptoms (7), activities of daily living (17), sport and recreation function (5), knee-related quality of life (4)
- Score on Likert scale: 0 (none) to 4 (extreme)
- Normalized score is calculated for each subscale: 100 (no symptoms) to 0 (extreme symptoms)
- Overall score: mean of 5 subscales
- Minimal clinically important difference: 8 to 10 points
- Responders: achieving at least 8 or at least 10 point improvement in overall KOOS from baseline

Modified Lysholm score

- 7 questions: pain, instability, locking, limp, stair climbing, squatting, support
- Scale: 0 to 24 (no symptoms or disability)
- Completed by study investigator from patient's self-report

Key outcome measures (2)

IKDC Current Health Assessment Form

- Patient self-report: symptoms, knee function and range of motion in past 4 weeks
- Scale: 0 to 100 (no limitations to daily or sports activities and absence of symptoms)

Magnetic resonance observation of cartilage repair tissue (MOCART)

- 9 categories: degree of defect repair and filling, integration to border zone, surface, structure and signal intensity of repair tissue, subchondral lamina and bone, adhesions, effusion/synovitis
- Scale: 0 (worst possible case) to 100 (normal)
- Independent radiologist (no information on treatment received)

ICRS visual histological assessment scale

- 6 items: surface, matrix, cell distribution, cell population viability, subchondral bone, cartilage mineralisations
- Score: 0 (poorest repair result) to 3 (truly regenerated tissue)

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)

Network meta-analysis

ACI (chondrosphere, chondrocelect, VeriMACI), microfracture

COWISI and Phase 2: Study characteristics

	COWISI (n=102) Chondrosphere vs microfracture	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 (bone grafting if bone loss >3mm)
Key inclusion/exclusion	no defects in both knees, instability, misalignment >5°; 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: Year 2	Primary outcome: 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 and Phase 2: Participant flow and analysis sets

	COWISI			Phase 2
	Chondrosphere	Microfracture	Total	Total
Randomised (safety population)	52	50	102	[redacted]
Baseline values recorded (ITT2)	49	50	99	[redacted]
Adequate cell growth or microfracture performed (ITT1)*	48	49	97	[redacted]
No major protocol violations	[redacted]	[redacted]	[redacted]	[redacted]

ITT: intention-to-treat
*used in analyses and presented results

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
  - Risk of bias from lack of blinding: limited by patient self-administered outcomes
- Non-inferiority rather than superiority design
  - Non-inferiority margin of 8.5 KOOS points
    - Company: COWISI designed in 2010 based on Saris et al (2008; ChondroCelect trial) which used a non-inferiority margin of -9.0. Roos et al (2003) suggests 10 points is the minimal clinically important difference (MCID) for KOOS. KOOS user guide suggests the MCID is 8-10 points
    - ERG: inadequately justified in terms of other possible benefits that counteract loss of efficacy
- Generalisability
  - Company: COWISI generalisable to UK NHS patients

COWISI – Results (ITT1 population)

[redacted]

Outcome at 2 years	Chondrosphere (n=48)	Microfracture (n=49)
Overall KOOS (mean ± SD)*	[redacted]	[redacted]
Change from baseline in overall KOOS (mean ± SD)*[a]	[redacted]	[redacted]
Responders (≥8 point improvement in KOOS)	[redacted]	[redacted]
Responders (≥10 point improvement in KOOS)	[redacted]	[redacted]
Overall MOCART scores^	[redacted]	[redacted]
Mean change from baseline in modified Lysholm score[a]	[redacted]	[redacted]

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

^No baseline MOCART scores were collected

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

Non-inferiority of chondrosphere vs microfracture (margin 8.5 KOOS)

- Company performed 3 tests: repeated measures ANCOVA ([redacted], $p<0.0001$, lower bound [redacted]), ANOVA (6.2), Satterthwaite test ([redacted], $p=0.0003$, lower bound [redacted])

COWISI – Histological assessment

[redacted]

Matrix (ICRS visual histological assessment) at 2 years	Chondrosphere (n=10)	Microfracture (n=7)
Hyaline	[redacted]	[redacted]
Hyaline/fibrocartilage	[redacted]	[redacted]
Fibrocartilage	[redacted]	[redacted]
Fibrous tissue	[redacted]	[redacted]

[redacted]

COWISI – KOOS results for post hoc subgroup analysis for defect size (ITT1 population)

[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])
Overall KOOS*	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in overall KOOS (median [IQR])*	[redacted]	[redacted]	[redacted]	[redacted]
Non-inferiority test (least square mean difference; t-test)		[redacted]		[redacted]

[redacted]

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Phase II – KOOS results (ITT1 population)

[redacted]

Mean ± SD change from baseline in overall KOOS at	Low dose (3-7 spheroids/cm²) (n=24)	Medium dose (10-30 spheroids/cm²) (n=25)	High dose (40-70 spheroids/cm²) (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, osteoarthritis, avascular necrosis, other diagnoses), defect location (femur, tibia, patella), age (18-34, 35-50) and sex did not show any systematic trends to explain any observed treatment differences

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
Male (%)	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

MF: microfracture

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	Treatment failure	Time point
COWISI (Chondrosphere)	≥10 point improvement in overall KOOS	Objective clinical findings and worsening of overall KOOS and subdomains: need for revision surgery	2 years
TIG/ACT (Chondro Celect)	≥10 improvement in overall KOOS ± ≥10 point improvement from baseline in ≥3 KOOS subdomains ± improvement from baseline in knee disorder severity ≥1 category or decrease from baseline 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 point 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"

- Uncertainty around comparability of trials. Company's qualitative assessment:
  - Mean lesion sizes: SUMMIT >4cm^2, COWISI and TIG/ACT <2.5cm^2
  - KOOS: SUMMIT moderate to severe KOOS pain subscores (<55) at baseline compared to COWISI and TIG/ACT
  - Follow up: COWISI and SUMMIT 2 years, 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

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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

Data input in network meta-analysis						
	Chondrosphere (n=48)	MF (n=49)	ChondroCelect (n=41)	MF (n=50)	VeriMACI (n=72)	MF (n=72)
Responders*	[redacted]	[redacted]	34	31	63	49
Treatment failed*	[redacted]	[redacted]	2	7	0	2
Time point	2 years		3 years		2 years	

MF: microfracture; *Number of patients

Adverse effects

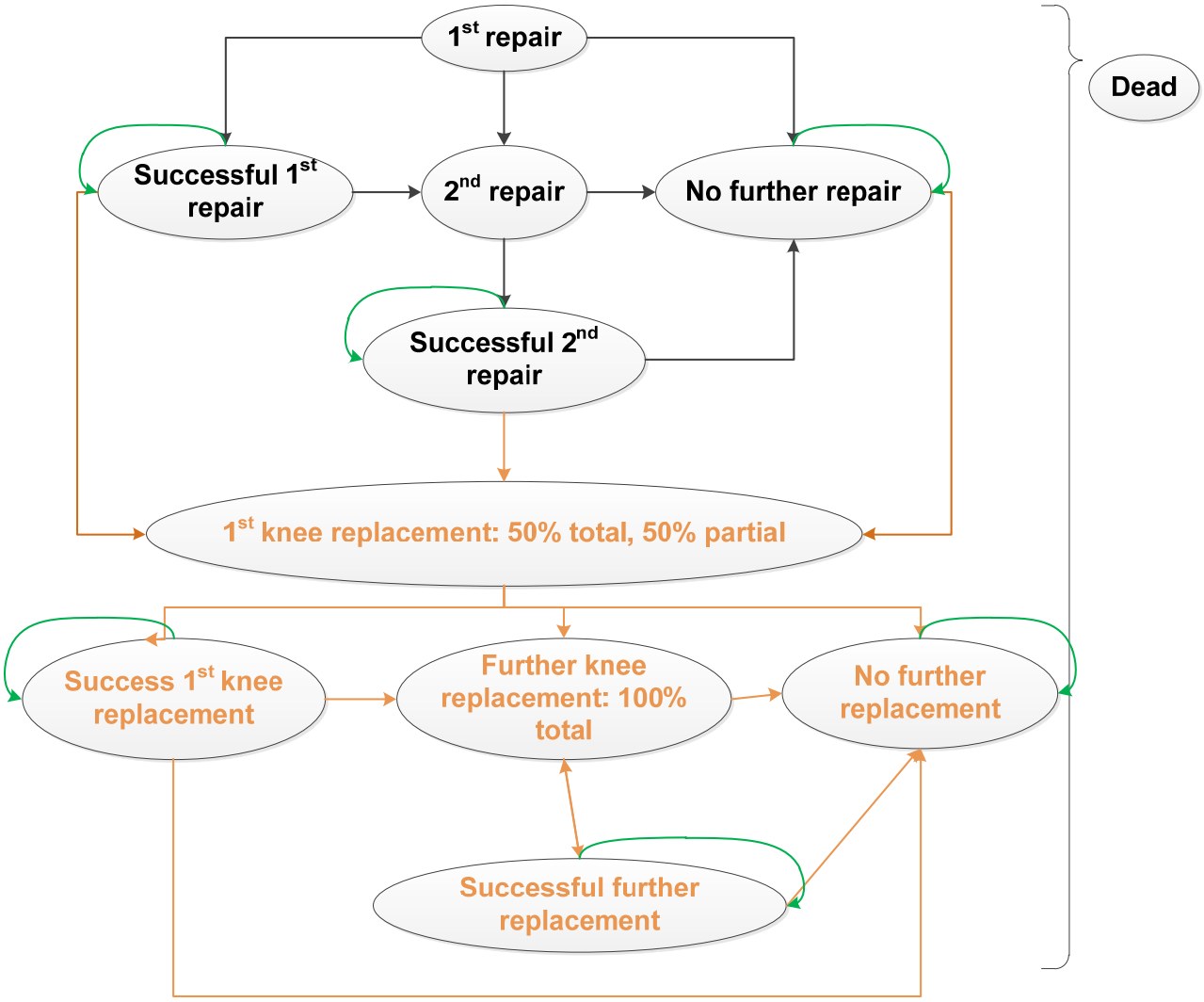
[redacted]

	COWISI		Phase 2 (n=[redacted])
	Chondrosphere (n=52)	Microfracture (n=50)	
Any adverse event	[redacted]	[redacted]	NR
Any serious adverse event	[redacted]	[redacted]	[redacted]
Any treatment-related adverse event	[redacted]	[redacted]	[redacted]
Withdrawals due to adverse events	[redacted]	[redacted]	[redacted]

[redacted]

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 microfracture return to baseline utility values at 5 years**

Company model – treatment sequences

Sequences	Treatment 1 (all patients)	Treatment 2 (only people needing repairs after treatment 1 receive treatment 2 [small proportion])
microfracture→ microfracture	microfracture	microfracture
microfracture→ ACI	microfracture	ACI can be chondrosphere, ChondroCelect or VeriMACI
ACI→ microfracture	ACI can be chondrosphere, ChondroCelect or VeriMACI	Microfracture
ACI→ACI	ACI can be chondrosphere, ChondroCelect or VeriMACI	Assumed to be the same ACI received for treatment 1

ACI: autologous chondrocyte implantation

- ERG comments:
  - Unlikely to have 2nd microfracture if 1st microfracture is not successful (TA477)
  - TA477 recommends ACI for people with no previous knee repair surgery (such as procedures that damage the subchondral bone [microfracture])
  - Relevant comparators are: microfracture only, ACI→microfracture, ACI→ACI

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	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 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	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 KR (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 difference compared with 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
  - Overstate treatment benefits for ACI compared with TA477 model (see table)

	Company model		1st AG report (table 16)		3rd AG report (table 2)	
	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; ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

Company model

Inputs: Clinical effectiveness data

- Assumption: effectiveness of 1st repair = effectiveness of 2nd repair
- Company model treatment effectiveness using response rate data from COWISI and associated relative risks from network meta-analysis. ERG: did not agree with calculation methods
- 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)				
Response rate	[redacted]	80%	87%	87%
Non-response rate	[redacted]	20%	13%	13%
2nd repair needed (failure rate)	[redacted]	3.4%	1%	0%
Subsequent years (cycle adjusted trial probabilities)				
Response rate	90%	89%	93%	93%
Non-response rate	10%	10.6%	6.7%	6.8%
2nd repair needed (failure rate)	1.25%^	1.72% [ERG: 1.73%]	1.25%^	1.25%^

*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.

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

	Company input and/or calculations	ERG comments
Successful 1st repair to 2nd repair	2 year trial data and network meta-analysis (adjusted to 1 year model cycle)	Cost effectiveness estimates worse for ACI than MF
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

Transition probabilities (knee replacement health states – over 55 years)

- Transition probabilities for knee replacement health states taken from TA477

	1st knee replacement	Further knee replacements
Probability occurring	1.01%	1.01%
Probability of associated death (TA477)	0.7%	1.1%
Probability of failing and receiving no further treatment	0.2%	2.09%
Probability of failing and further knee replacement	0.58%	NA

NA: not available

Company model
Inputs: Health utilities data for repairs

- Taken from TA477
- Assumption: utilities for chondrosphere are equal to other ACIs in the model

	Company description	Source
1st repair	**Successful repair** ACI: higher utility while in this state MF: utility maintained up to year 5 after repair, then it falls to pre-repair level **No further repair:** some utility gain	Gerlier et al – SF36 data in TIG/ACT trial mapped to EQ-5D • baseline utility 0.654 • post-intervention utility 0.760 • full recovery after 1 cycle 0.817 [clinical success 5 years after surgery in Gerlier] • no further repair 0.691 [no clinical success 5 years after surgery in Gerlier])
2nd repair	Patients return to baseline utility before 2nd repair **No further repair:** same utility as people who do not have a 2nd repair following 1st repair **Successful repair** Conditional on 1st repair (ithat is, ACI or MF) ACI→ACI: utilities are same as 1st repair MF→ACI: utilities decrease after 4th year [average of year 1 post-intervention utility of 0.760 and clinical success after 5 years following intervention of 0.817 = 0.789] MF/ACI→MF: utilities are same as successful 1st repair	

Company model
Inputs: Health utilities data for knee replacements

- Taken from TA477
- Assumption: utilities for chondrosphere are equal to other ACIs in the model

	Company description	Source
Knee replacement (KR)	Not conditional on previous repair type Lower utilities than people needing repairs **Successful replacement:** increased utilities, same for 1st or further replacements **Further replacements:** utility drops to lowest value **No further replacements:** higher utility values than those who require further replacements	Dong and Buxton, Janssen and Granath – EQ-5D data: • baseline utility 0.615 [average utility from both studies] • successful 1st KR and further KR were the same at 0.780 [Dong and Buxton] • failed 1st KR and required further TKR: utility of 0.557*

*In the company's clarification response #2, it states that the utility value was amended to 0.691 as in TA477.

Company model
Inputs: Health utilities – 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**

	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

Company model
Inputs: Health utilities – 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: QoL 0.615
Further knee replacement: QoL 0.691
*ERG: TA477 applies 0.691. Lower utility disadvantages sequences that result in more knee replacements

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

Company model
Inputs: Resources and costs

	Chondrosphere	Chondro Celect	VeriMACI	Microfracture	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

P/TKR: partial/total knee replacement

Company model – base case deterministic, fully incremental results

	Cost	QALYs	∆ Cost	∆QALYs	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

ERG exploratory analysis

	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 (as above) in 1 model cycle
Comparators probability of 2nd repairs	1 minus 2 year probabilities of response	Multiply chondrosphere probability of 2nd repair by comparators' relative risks of 2nd repair
Microfracture probability of 2nd repair	1.72%	Remove double halving of 2 year probability; 3.44%
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 vs maintained at 5 years
Knee replacement to no further replacement QoL values	0.691 or 0.557	0.691 only
Costs of ACI	£734 and £1,065	£870 and £2,396

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

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

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)
  - Benefit of ACI is likely to be seen over longer-term (TA477 observational studies)
  - Clinical effectiveness observed in TIG/ACT and SUMMIT trials may be explained by the differences in patient characteristics

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)

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

Authors

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- with input from the Lead Team (**Ray Armstrong, John Cairns, Nigel Westwood**)

Additional slides

UK Consensus statement of 104 clinicians (2015) (1)

- Articular cartilage lesions – usually on femoral condyles; can result from trauma, other conditions (osteochondritis dissecans), previous sepsis, inflammation; symptoms include pain, swelling, catching, locking, instability. Arthroscopy (gold standard) for assessing lesion size and functional integrity of surrounding cartilage. Articular cartilage – limited capacity for self-repair in adults, lesions >9mm are biomechanically unstable and will progress to degeneration of joint surface (OA)
- Treatment options after conservative management (specialised lower limb physiotherapy and rehabilitation, activity modification, weight management) is inadequate for isolated defect of knee that is stable, surgically stabilised by ligament reconstruction where alignment is normal or surgically corrected by osteotomy, free from inflammatory joint disease and some functional meniscal tissue intact.
- **Bone marrow stimulation techniques** (microfracture, augmented microfracture, drilling): bone in base of defect is multiply piered and allowed to bleed. Cells in blood clot form fibrous scar tissue (type 1 collagen), has poorer biomechanical properties and purported to degenerate by around 24 months. Poorer outcomes in medium term for active patients or larger defects

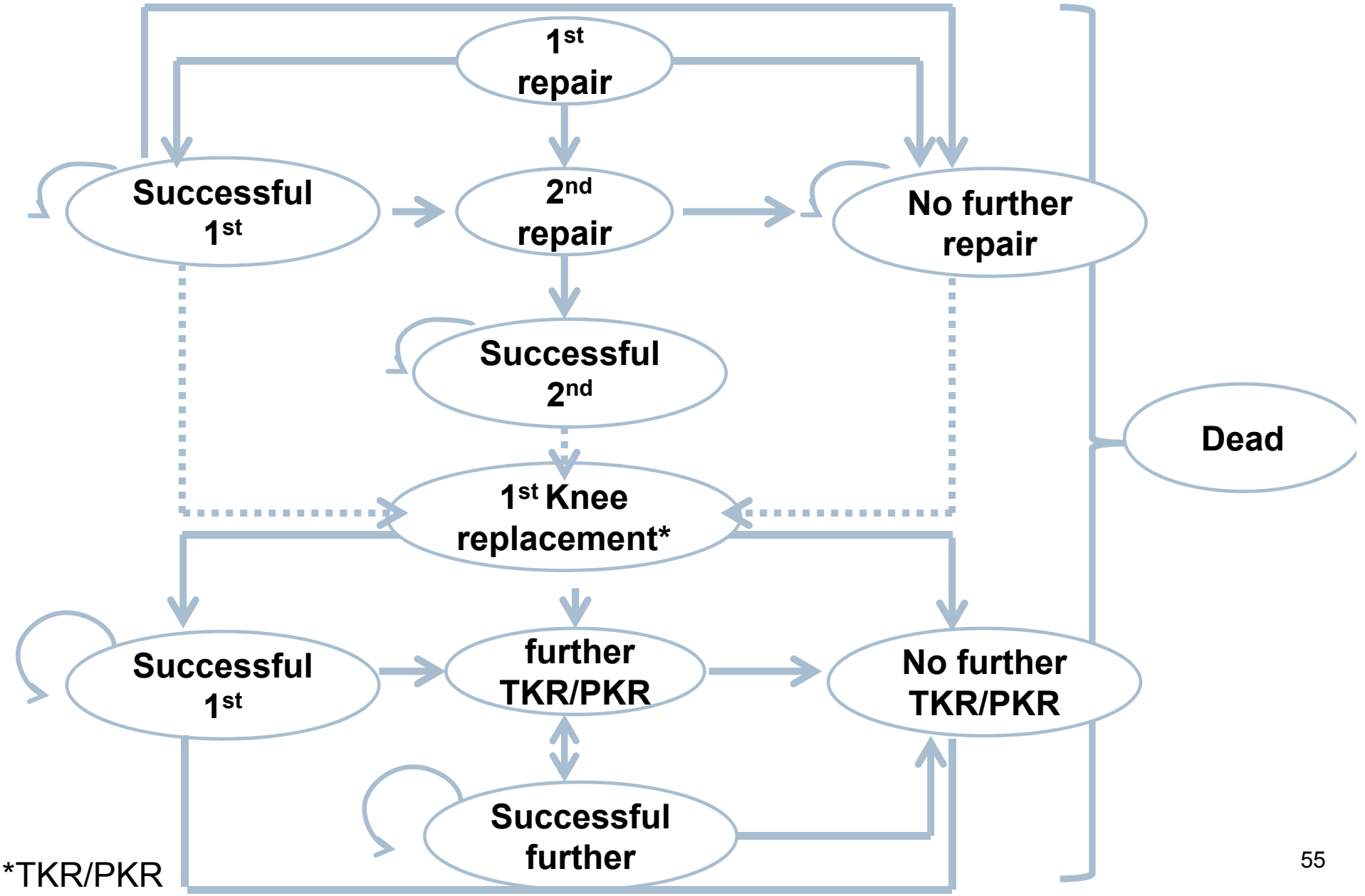
UK Consensus statement of 104 clinicians (2015) (2)

- Osteochondral grafting. Autologous intact articular cartilage and underlying bone is harvested from area of knee less involved in weight bearing and implanted into defect of same knee. Bony element heals well, good short term outcome, poor integration of graft. Poorer outcomes at medium and long term. Larger defects need multiple plugs and patellar lesions have poor outcomes.
- Osteochondral scaffold. Matrices are implanted into the defects and cells migrate into the scaffold. Bone marrow stimulating techniques may be used as a source of cells. No RCTs or long-term cohort studies.
- Cell therapy (autologous chondrocyte implantation). Small biopsy of cartilage harvested from area of minimal weight bearing or defect. Cartilage is enzymatically digested in laboratory to release chondrocytes, that are cultured and returned for implantation into the defect at a 2nd surgery.
- 1st generation: 1987 introduction of technique used periosteum as a patch under which cells were injected. Periosteum prone to hypertrophy. Techniques now use collagen patch, either as a cover for injected cells or a structure to be preloaded with cells. ACI is worse if performed after bone marrow stimulation techniques with a 6-fold increase in failure rate of ACI after previous microfracture.
- Poorer outcomes in smokers, BMI >30, long duration of preoperative symptoms. Size of defect must be considered in relation to size of knee.

UK Consensus statement of 104 clinicians (2015) (3)

- Treatment options based on lesion size following debridement of non-functional damaged cartilage tissue as primary determinant:
  - Symptomatic contained defects <2cm^2 in an average sized knee: bone marrow stimulation techniques, osteochondral grafting
  - 2-4cm^2 in an average sized knee: cell therapy. Poor intermediate results after bone marrow stimulation techniques, and high donor site morbidity after osteochondral grafting procedures
  - >4cm^2: no bone marrow stimulation techniques or autologous osteochondral grafting procedures. Cell therapy or allograft osteochondral grafting
- .Treatment options based on lesion location:
  - Osteochondral cylinder transfer is suboptimal in patellofemoral joint; do not use if 1 plug is required. Articular cartilage of patella is thickest, low volume of bone marrow. Microfracture has poorer outcomes in patella compared to other parts of knee. For a normally tracking patella, cell therapy is effective.
- Treatment failure: poor patient-reported outcome score and objective evidence of failure on imaging or arthroscopic assessment.

Model structure – Assessment Group TA477



*TKR/PKR

COWISI – KOOS subscales results (ITT1 population)

	Mean ± SD change from baseline at 24 months		Repeated measures ANCOVA difference (lower confidence interval limit)
	Chondrosphere (n=48)	Microfracture (n=49)	
Overall	[redacted]	[redacted]	[redacted]
Symptoms	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Function in daily living	[redacted]	[redacted]	[redacted]
Function in sport and recreation	[redacted]	[redacted]	[redacted]
Knee-related quality of life	[redacted]	[redacted]	[redacted]

COWISI – IKDC current health assessment subscale results (ITT1 population)

	Mean ± SD change from baseline at 24 months		Chondrosphere vs microfracture *p* value
	Chondrosphere (n=48)	Microfracture (n=49)	
Physical functioning	[redacted]	[redacted]	[redacted]
Role physical	[redacted]	[redacted]	[redacted]
Bodily pain	[redacted]	[redacted]	[redacted]
General health	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Role emotional	[redacted]	[redacted]	[redacted]
Mental health	[redacted]	[redacted]	[redacted]
Physical component summary	[redacted]	[redacted]	[redacted]
Mental component summary	[redacted]	[redacted]	[redacted]

*$p<0.05$

^$p>0.05$

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of chondrosphere within its marketing authorisation for treating articular cartilage defects.

Background

Articular cartilage is hyaline cartilage on the joint surfaces of the bone. Articular cartilage defects can be caused by injury (often sports related), or arthritis, or it can occur spontaneously. Cartilage damage may also arise because of instability or abnormal unbalanced pressures in the joint. Damage of the articular cartilage does not heal on its own and can cause symptoms such as pain, swelling, locking and giving way of the joint. In addition, damage to the cartilage and surrounding tissues can cause osteoarthritis and lead to a need for partial or total joint replacement surgery in later life. Cartilage damage can be described by size (area) and graded by depth. Commonly used scoring systems include the international cartilage repair society (ICRS) grading system, and the Outerbridge system.

There are no reliable estimates of the prevalence of symptomatic articular cartilage defects, although it is estimated that around 10,000 people need treatment for cartilage damage every year in the UK.

The aim of treatment is to relieve symptoms such as locking, swelling, and instability, and to improve general mobility. Treatment options include debridement (removal of damaged cartilage), re-establishing the articular surface (microfracture, mosaicplasty and autologous chondrocyte implantation), osteotomy, and joint replacement. Osteotomy and joint replacement are options reserved for larger lesions and those where cartilage repair has failed.

In autologous chondrocyte implantation, healthy chondrocytes are harvested arthroscopically from the affected joint. The cells are cultured in a laboratory and then implanted into the damaged areas of the cartilage. The method for delivering the cells to the damaged area has evolved over time. The number of people with symptomatic cartilage defects suitable for autologous chondrocyte implantation is estimated to be between 200 and 500 people each year in the UK.[1]

NICE technology appraisal 89 does not recommend autologous chondrocyte implantation for the treatment of articular cartilage defects of the knee except

in the context of ongoing or new clinical studies. NICE interventional procedure guidance recommends mosaicplasty (IPG162) and microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects (IPG560) be used with special arrangements for clinical governance, consent and audit or research.

The technology

Chondrosphere (Co.don) is a technique in which the cartilage is developed in vitro. Cultured chondrocytes are seeded into agarose to form stable chondrocyte aggregates (spheroids). These spheroids, or 'microtissues' are induced to form cartilage-like tissue and are grown in vitro for 8 to 10 weeks. The resultant 'chondrospheres' are then transplanted into the defect.

Chondrosphere does not currently have a marketing authorisation in the UK for people with articular cartilage defects. It has been studied in trials in adults with cartilage defects of knee joints.

Intervention(s)	Chondrosphere
Population(s)	People with articular cartilage defects
Comparators	As appropriate for lesion size: • Microfracture (marrow stimulation) • Autologous chondrocyte implantation (subject to ongoing NICE appraisal) • Knee debridement • Mosaicplasty • Best supportive care (non-operative intervention)
Outcomes	The outcome measures to be considered include: • pain • joint function including long-term function • rates of retreatment • activity levels • avoidance of osteoarthritis including joint replacement • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If the evidence allows consideration will be given to subgroups stratified by duration of symptoms, size and site of lesion, previous exposure to surgical treatment, and for cartilage defects secondary to malalignment.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: The use of autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89). NICE technology appraisals guidance (ID686). Publication expected: September 2017. Autologous chondrocyte implantation (ACI) for the treatment of cartilage injury (review of Technology Appraisal 16) (2005). NICE technology appraisals guidance 89. Under review. Related Interventional Procedures: Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects (2016). NICE interventional procedures guidance 560. Mosaicplasty for knee cartilage defects (2006). NICE interventional procedures guidance 162. Related NICE Pathways: Musculoskeletal conditions (2017) NICE pathway http://pathways.nice.org.uk/
Related National	NHS England, Manual for Prescribed Specialised

Policy	Services 2016/17 (published 2016): Chapter 13. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf

References

1. NIHR Horizon Scanning Centre (2014) Spheroids of human autologous matrix-associated chondrocytes (chondrosphere) for articular cartilage defects. Birmingham: NIHR Horizon Scanning Centre.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Co.don AG (chondrosphere) Patient/carer groups • Action on Pain • Arthritis Action • Arthritis & Musculoskeletal Alliance • Arthritis Care • Disability Rights UK • Leonard Cheshire Disability • Muslim Council of Britain • Pain Concern • Pain Relief Foundation • Pain UK • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Anaesthetists • Association of Surgeons of Great Britain and Ireland • British Association for Surgery of the Knee • British Association of Day Surgery • British Geriatrics Society • British Institute of Musculoskeletal Medicine • British Institute of Radiology • British Orthopaedic Association • British Pain Society • British Society for Gene and Cell Therapy • British Society for Rheumatology • British Society of Rehabilitation Medicine	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • ACI (Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust) • Vericel (Matrix applied characterised autologous cultured chondrocyte implant – MACI) Relevant research groups • Arthritis Research UK • Bone Research Society • Chronic Pain Policy Coalition • Cochrane Musculoskeletal Group • MRC Clinical Trials Unit • National Institute for Health Research • UK Stem Cell Foundation

Consultees	**Commentators (no right to submit or appeal)**
• British Trauma Society • Chartered Society of Physiotherapy • Physiotherapy Pain Association • Primary Care Rheumatology Society • Rheumatoid Arthritis Surgical Society • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS England • NHS Bexley CCG • NHS Central Manchester CCG • Welsh Government	<u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland;; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document A

Company evidence submission summary for committee

Co.don confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

December 2017

File name	Version	Contains confidential information	Date
Spherox_ID581_DocumentA_18DEC17	1.0	No	18th December 2017

Contents

Tables and figures

Submission summary

A.1 Health condition (Document B, B.1, B.1.3, p17)

Articular cartilage provides a smooth, lubricated surface for articulation at synovial joints. It is a specialized connective tissue that comprises hyaline and that lacks blood vessels, lymphatics, and nerves. Articular hyaline cartilage is 2 to 4-mm thick and is composed of a dense extracellular matrix (ECM) with a sparse distribution of chondrocytes – specialized cells involved in the development, maintenance, and repair of the ECM.

Articular cartilage injuries are precursors to long-term musculoskeletal morbidity, particularly as cartilage has a limited capacity for healing and repair. Consequently, treatment and repair or restoration of articular cartilage are challenging for the patient, the surgeon, and the physical therapist.

Articular cartilage defects can be caused by injury, or wear and tear leading to osteoarthritis. Cartilage damage may also arise because of knee instability or abnormal unbalanced pressures. Obesity may also cause osteoarthritis in knee cartilage and hip damage due to excessive weight-bearing. Condylar or patellar defects often become symptomatic and if they persist progress to secondary osteoarthritis, which affects daily living activities and quality of life.

A.2 Clinical pathway of care (Document B, B.1, B.1.3, p17-18)

In the UK, patients with symptomatic articular cartilage defects in the knee will first be offered best supportive care (BSC) before surgical interventions. BSC options include, but are not limited to, weight loss, physiotherapy, corticosteroid injections, and pain medication. If symptoms persist, the patient will be considered for reparative/restorative procedures which may include knee lavage (with or without debridement, the removal of damaged cartilage), microfracture (MF), mosaicplasty, and autologous chondrocyte implantation (ACI). Osteotomy (realigning of the knee) and knee replacement are surgical options reserved for larger lesions and those where cartilage repair has failed. In the UK, the main options currently are MF, mosaicplasty and ACI; the selection of the procedure depends on a range of patient-related factors (history of surgery, age, BMI) and condition of the damaged cartilage

(including lesion size). ACI is the preferred choice in UK clinical practice, however, due to access issues MF is the most common procedure performed. If symptoms persist after MF or ACI, other interventions will be considered, including mosaicplasty or ACI. MF would not be preferred as a second intervention if MF was previously performed. Knee replacement (total and partial) are only considered as the last treatment option in UK clinical practice if osteoarthritis develops.

A.3 Equality considerations (Document B, B.1, B.1.4, p19-20)

Spherox contains no animal derivatives nor any additional delivery mechanisms of animal origin. Therefore, there is no patient exclusion based on ethical, moral, or religious grounds.

Paediatric population

In concordance with the PIP (EMEA-001264-PIP01-12), a prospective non-interventional investigation (cod 16 HS17 paed) was initiated to evaluate the long-term safety and efficacy of the ACT3D product in adolescents from 15 to 17 years of age (inclusive) treated with the commercial product up to December 2011.

Two studies, cod 16 HS 16 (2012) and cod 16 HS 17 paed (2016), have demonstrated that ACT3D using Spherox was considered suitable, safe and effective for the treatment of cartilage defects of the knee in adolescents of 14 to 17 years of age. In total, 58 adolescents were investigated in both studies. An overlap of 12 patients between cod 16 HS16 and cod 16 HS17 paed were found.

Older people:

In clinical practice, patients up to 55 years of age have usually been treated. Clinical data of adult patients aged over 55 years are limited. The application of Spherox in patients older than 50 years has not been studied. Applying Spherox to older patients with advanced cartilage degeneration or osteoarthritis is not recommended.

A.4 The technology

Table 1 Technology being appraised – (Document B, B.1, B.1.2, p14)

UK approved name and brand name	Spherox
Mechanism of action	The mode of action of Spherox is based on the removal of the patient's own chondrocytes isolated from healthy cartilage, their culture in vitro and their subsequent implantation into the cartilage defect. Spherox is cultured and implanted as three-dimensional spheroids. Spherox uses a technique in which the cartilage is developed in vitro. Cultured chondrocytes are seeded into agarose to form stable chondrocyte aggregates (spheroids). These spheroids, or "microtissues" are induced to form hyaline like cartilage tissue and are grown in vitro for 6 to 8 weeks. The resultant spheroids are then transplanted into the defect.
Marketing authorisation/CE mark status	The European Medicines Agency (EMA) granted Spherox marketing authorisation on 10 July 2017. The approved indication is for 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 cm2 in adults. The treatment of defect sizes up to 10 cm2 is eligible for single as well as adjacent defects (combined area). CO.DON AG develops, produces, and markets autologous cell therapies for the minimally invasive repair of cartilage damage to joints following traumatic or degenerative defects. Spherox is a cell therapy product that uses only the patient's own cartilage cells ("autologous chondrocytes") and has been approved by the German federal agency PEI in accordance with Section 4b of the German Pharmaceuticals Act (AMG). The technology, marketed under the name co.don chondrosphere, has been used for more than 10 years in over 120 clinics to treat more than 11,000 patients.
Indications and any restriction(s) as described in the summary of product characteristics	The approved indication is for 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 cm2 in adults. The treatment of defect sizes up to 10 cm2 is eligible for single as well as adjacent defects (combined area). Spherox is an autologous product and should not be given to any other patient than the donor. Spherox is not recommended in children or adolescents below 18 years. Spherox is not recommended for pregnant or breast-feeding women. Contraindications • Patients with not fully closed epiphyseal growth plate in the affected joint. • Primary (generalised) osteoarthritis.

	• Advanced osteoarthritis of the affected joint (exceeding grade II according to Kellgren and Lawrence). • Infection with the hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV I/II viruses.
Method of administration and dosage	Spherox is intended exclusive for use in a matrix-associated ACI (ACI-M). The implantation must be performed during a surgical procedure (preferably an arthroscopy or mini-arthrotomy). A debridement of the defect area is required. The subchondral plate should not be damaged. The spheroids are provided in a pre-filled syringe or an applicator (stem length 150 mm or 250 mm, co.fix® 150 or 250, respectively). Spheroids should be applied evenly on the defect ground and, if necessary, spread over the whole defect area by means of surgical instruments. The spheroids self-adhere within 20 minutes onto the defect ground. Afterwards, the surgical wound can be closed without any additional cover, e.g., periosteal flap of the treated area, or any fixation of spheroids by using fibrin glue. Patients treated with Spherox have to undergo a specific rehabilitation program. The program may take up to one year, depending on the recommendation of the physician. *Posology:* 10–70 spheroids are applied per square centimetre defect. *General*: Spherox is an autologous product and should not be given to any other patient than the donor. Prior to use, verify if the patients name matches the information of the patient/donor provided on the shipping documents and the product label. Also check if the correct order number (lot number) is on the primary package. If the primary or secondary packaging is damaged and therefore unsterile, Spherox should not be applied. *Paediatric population*: Before a cartilage defect in an adolescent patient is treated it has to be radiologically confirmed that the epiphyseal growth plate is closed. *Precautions for use*: Patients with local inflammations or acute as well as recent bone or joint infections should be deferred until the recovery from the infection. If possible, concomitant joint diseases should be corrected prior to or at the latest, at the time of Spherox implantation. *Rehabilitation*: After implantation, the patient should follow an appropriate rehabilitation schedule. Physical activity should be resumed as recommended by the physician. Too early and vigorous activity may compromise the grafting and the durability of clinical benefit from Spherox.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	£10,000
Patient access scheme (if applicable)	Previously, a confidential price of [redacted] was agreed with the Department of Health but this was specifically for an early access scheme and only relates to unlicensed co.don chondrosphere.

A.5 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication.

The technology is Spherox, a 4th generation autologous chondrocyte implantation (ACI) technique licenced for 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. The treatment of defect sizes up to 10 cm^2 is eligible for single as well as adjacent defects (combined area).

The decision problem is summarised in **Table 2** below.

The population considered in the decision problem is adults with articular cartilage defects, in line with the final scope.

The comparators considered in the decision problem are microfracture (MF) and other ACIs (MACI and ChondroCelect), which were included in the final scope. Other comparators included in the scope issued by NICE were considered not relevant for the target population or not currently used in the UK.

The outcomes of the decision problem are the same as the final scope except for the exclusion of adverse events, which were not considered.

Table 2 The decision problem – (Document B, B.1, B.1.1, p13)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with articular cartilage defects	Adults with articular cartilage defects	N/A
Intervention	Spherox	Spherox	N/A
Comparator(s)	Microfracture (marrow stimulation) ACI (subject to ongoing NICE appraisal) Knee debridement Mosaicplasty Best supportive care (non-operative intervention)	Microfracture ACI (MACI and ChondroCelect)	Some of the initially stated comparators were considered not relevant for the target population or not currently used in the UK
Outcomes	Pain, knee function including long-term function, rates of re-treatment, activity levels, avoidance of	Pain, knee function including long-term function, rates of re-treatment, activity levels, avoidance of	N/A

	osteoarthritis including knee replacement, adverse effects of treatment, health-related quality of life	osteoarthritis including knee replacement (incorporated into economic modelling only), health-related quality of life	
Economic analysis	Cost effectiveness to be expressed in terms of incremental cost per quality-adjusted life year	Cost effectiveness to be expressed in terms of incremental cost per quality-adjusted life year	N/A
Subgroups to be considered	N/A	N/A	N/A
Perspective for outcomes	N/A	N/A	N/A
Perspective for costs	NHS and Personal Social Services perspective	NHS and Personal Social Services perspective	N/A
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	N/A
Synthesis of evidence on health effects	Systematic literature review	Systematic literature review	N/A
Measuring and valuing health effects	Quality adjusted Life years (QALYs)	Quality adjusted Life years (QALYs)	N/A
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities were sourced directly from patients used either the EQ-5D or the SF-36 and mapped to the SF-6D	N/A
Source of preference data for valuation of changes in health-related quality of life	Reported directly by patients and/or carers	In Janssen and Granath preference scores generated from the UK population was used. It is not clear if this was used in the remaining source.	Due to availability of utility data in the target patient population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	N/A
Evidence on resource use and costs	Costs refers to the cost incur by NHS to treat the condition.	Costs refers to the cost incur by NHS to treat the condition. Only direct costs were included	N/A
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The same annual rate for both costs and health effects (currently 3.5%)	N/A

A.6 Clinical effectiveness evidence

This submission is based on a prospective, randomised, open label, multicentre Phase III clinical trial designed to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product Spherox with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm2. In addition, the phase II trial for the same technology, defect sizes between 4 and 10 cm2, has been summarised in order to provide a complete overview of the clinical trial program in patients with knee cartilage defects.

Table 3 Clinical effectiveness evidence of Phase III trial – (Document B, B.2, B.2.2, p21)

Study title	NCT01222559 (COWISI) (2017)
Study design	Prospective, randomised, open label, multicentre Phase III clinical trial
Population	The analysis population comprised 102 patients (41 women, 61 men) aged 37 ± 9 years.
Intervention(s)	Implantation of three-dimensional autologous chondrocyte implantation product (Spherox) into the cartilage defect, resulting in hyaline cartilage repair. There are two study interventions: a single arthroscopy including harvesting of chondrocytes and, after approximately 2 months, a single implantation of the study product Spherox.
Comparator(s)	Marrow-stimulating method (microfracture)
Outcomes specified in the decision problem	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from Day 0 (baseline for both treatment groups = pre arthroscopy assessment) to final assessment (FA) 24 months after the end of the respective treatment, compared between the two study treatment groups (Spherox and microfracture). The 36 , 48 and 60 month visits are follow-up visits. Overall KOOS including 5 Subscores (Pain, Knee function including long-term function, activities of daily living, other symptoms and quality of life). Activity levels, avoidance of osteoarthritis including knee replacement, adverse effects of treatment, health-related quality of life.
Reference to section in submission	B.2.2 p21; B.2.3.1 p23-33; B.2.4.1 p40-46; B.2.6.1 p50-68; B.2.7.1 p72; B.2.10.1 p83-88;

Table 4 Clinical effectiveness evidence of Phase II trial – (Document B, B.2, B.2.2, p22)

Study title	Trial no. cod 16 HS 14
Study design	Prospective, phase II, multicentre, randomised, open label (central radiologist as blind observer for MRI), dose-response study.
Population	Male and female patients between ages of 18 and 50 years with an isolated single cartilage defect of the knee joint

Intervention(s)	Product ACT3D-CS = autologous chondrocyte product Spherox Group A: ACT3D-CS in patients receiving 3-7 spheroids/cm2 Group B: ACT3D-CS in patients receiving 10-30 spheroids/cm2 Group C: ACT3D-CS in patients receiving 40-70 spheroids/cm2
Comparator(s)	N/A
Outcomes specified in the decision problem	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from baseline to final assessment at 12 months (after implantation). The 24, 36-, 48- and 60-month visits are follow-up visits.
Reference to section in submission	B.2.2 p21; B.2.3.1 p23-33; B.2.4.1 p40-46; B.2.6.1 p50-68; B.2.7.1 p72; B.2.10.1 p83-88;

Phase II trial (Trial no. cod 16 HS 14) was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study support the efficacy results of Spherox and offer long-term data (4 years) for efficacy and safety. This study was not included in the economic model because it is not comparative.

A.7 Key results of the clinical effectiveness evidence (Document B, B.2, B.2.13, p92-94)

A.7.1 *Overall KOOS score*

In the primary analysis, in the assessment of "overall KOOS" for the ITT1 population, both Spherox and microfracture yielded statistically significant improvements relative to baseline (Step 1). For the patients treated with Spherox the mean overall KOOS score rose from [redacted] at baseline to [redacted] at Visit 4 (12 months) and to [redacted] at Visit 6 (24 months), while for those treated by microfracture the score rose to [redacted] after 12 months and [redacted] after 24 months ($p < 0.0001$ for all).

According to the between-group primary analysis conducted for the 24-month results the Spherox treatment passed the test of significant non-inferiority compared with microfracture; thus the primary goal of the study was achieved. Repetition of the primary analysis with different study populations (PP, ITT2, observed cases) gave similar results.

The KOOS subscores yielded the same qualitative result as the full-KOOS analysis. Although improvements with respect to baseline were in each case greater for the

Spherox than for the microfracture group. Superiority was not demonstrated for the Overall KOOS with descriptive statistical significance.

A.7.1 *Overall MOCART score*

The results for all other secondary variables supported those of the KOOS analyses. The overall MOCART score showed improvements from Visit 2 to Visit 4 (3 to 12 months) with a further improvement to Visit 6 (24 months) in both treatment groups. The MOCART score was [redacted] for the Spherox group and [redacted] for the microfracture group at Visit 2, improving respectively to [redacted] at Visit 4 and to [redacted] at Visit 6. The slightly better result for the Spherox group should, however, be interpreted with caution as no baseline MOCART scores were available for comparison. The individual MOCART items showed variable differences with regard to treatment response and also to the difference between treatment groups. The greatest improvements were observed in 1 (defect repair), 3 (surface), 5 (signal intensity), 7 (subchondral bone), and 9 (synovitis). A systematic difference between the two treatment groups could not be established.

A.7.1 *IKDC assessment*

The IKDC assessments and the Modified Lysholm score showed comparable improvements in both treatment groups; the improvement was generally slightly greater in the Spherox group baseline and Visit 4 (12 months), with a smaller difference at Visit 6 (24 months)

A.8 Evidence synthesis (Document B, B.2, B.2.9.2, p77-78)

Two outcomes have been included and investigated in this NMA: number of responders; and failure rate. Results for each of the above outcomes can be found below. Due to the small number of trials informing each comparison in the network, there was not enough evidence to reliably inform the heterogeneity parameter in the random effects model. Therefore, only results derived from the fixed effects model will be presented.

Number of responders:

The median RRs suggest that Spherox is associated with a higher number of responders when compared to MF ([redacted]) and with a lower number of responders when compared to MACI ([redacted]) and ChondroCelect

([redacted]). However, these results were not statistically significant with the 95% CrI crossing unity.

Failure rate:

The median RRs suggest that Spherox is associated with a lower failure rate when compared to MF ([redacted]) and ChondroCelect ([redacted]) and with a same number of failures when compared to MACI (no failures were observed in COWISI and SUMMIT). However, these results were not statistically significant with the 95% CrI crossing unity.

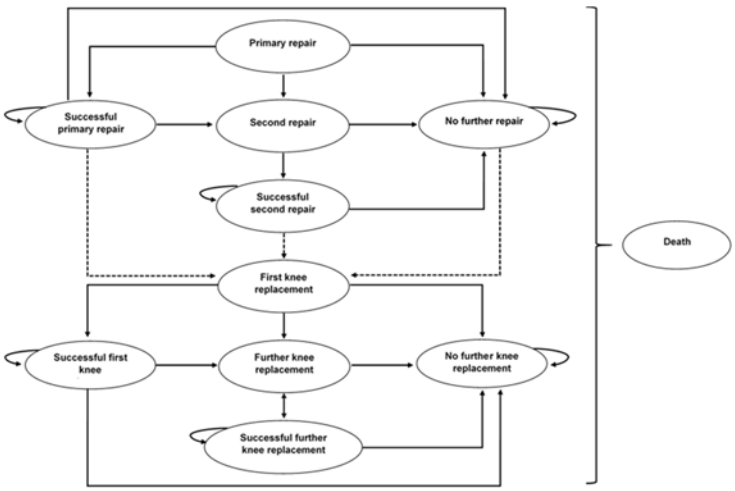
A.9 Key clinical issues

- Study powered for non-inferiority, not for superiority
- Imbalance between arms (MF and Spherox) in terms of baseline KOOS score
- High level of heterogeneity across the trials included in the indirect comparison

A.10 Overview of the economic analysis

The cycle length is one year which allows patients to recover from surgery. Transitions between each health state occur at the end of each cycle. A lifetime horizon is adopted.

Figure 1 Model diagram – B.3.2 (page 105)



A.11 Incorporating clinical evidence into the model

Trial and NMA data was cycle adjusted for implementation into the model as transition probabilities (i.e. the 2 year rates were converted to one-year probabilities) which are shown in transition matrices below which are categorised by age group (20-54 and 55+). Transition probabilities vary between age groups because patients become eligible to receive knee replacement at the age of 55.

Transition probabilities for success and failure for patients who received a knee replacement or knee replacement revision have been obtained from Mistry et al. It was assumed that transition probabilities for patients receiving a partial or total knee replacement were the same.

The data derived from trials and incorporating relative risks from the NMA apply to the lifetime of the model (as probabilities) except the failure rates for MACI and Spherox; these rates (0%) were used in the first two years of the model (the length of the trials) but did not seem reasonable to extrapolate to future years. A conservative estimate of 1.25% failure rate was used based on a similar assumption taken by Mistry et al (32). In Mistry et al, it was assumed that 12.5% of the non-responders will move to the no further repair health state and of these 12.5%, they assumed that 10% of them will move from the successful primary to the second repair health state (1.25%). This has been applied to the current analysis due to the lack of long term data. The same assumption has been applied to both Spherox and MACI, while fro MF and ChondroCelect, a proportion of patients report required a second surgery during the trial period. The same proportion of patients (adjusted by cycle length) has been assumed to be applicable for the all subsequent years in the economic model.

A.12 Key model assumptions and inputs

A full list of inputs used in the economic model can be found in Document B, B.3.6, p121-129. **Table 5** below summarises the key model assumptions.

Table 5 Key model assumptions and - (Document B, B.3, B.3.6, p129-130)

Model input and cross reference	Source/assumption	Justification
Time horizon	A lifetime horizon is appropriate for the base-case analysis	Shorter time horizons may not capture the full cost and/or benefits relevant to the decision problem. This time horizon is also modelled as the base case in

		other published analyses in the same disease area.
Clinical inputs	The efficacy of technologies derived from trials and NMA is generalisable to the proposed patient population in England and Wales.	Lack of data
Clinical inputs	The efficacy of technologies, except for some failure rate data (see Assumption 4), derived from trials and NMA is applicable for the patients' lifetime and is extrapolated over the entire time model horizon	Lack of data
Clinical inputs	The failure rate for MACI and Spherox from trials does not continue after year 2	Failure rates from the 2 year trial data from MACI and Spherox are 0%. It did not seem reasonable to extrapolate beyond the first 2 years of the model. In future years a 1.25% failure rate was used. This assumption is also taken by Mistry et al.
Clinical inputs	The efficacy of the technologies' after primary repair are equal to efficacy after secondary repair	Data is not available on the efficacy following secondary repair. This assumption is also taken by Mistry et al.
Clinical inputs	50%/50% PKR/TKR for first repair	This assumption is also taken by Mistry et al.
Utility values	Utilities from Mistry et al are applicable to this model	This provides consistency and comparability of technologies for the same indication.
Utility values	The utilities for Spherox are equal to other ACIs in the model	Data on patient HRQoL from Spherox trials is not available. This conservative assumption provides consistency and comparability of technologies.
Adverse events	Adverse events or complications are not considered	Adverse events or complications are assumed to have little impact on the outcomes of the analyses. This assumption is also taken by Mistry et al.

A.13 Base-case ICER (deterministic)

Results of the base-case incremental cost-effectiveness analysis for the average patient are shown in the table below. Treatment combinations (primary followed by secondary repair) are listed from least to most expensive, then ranked in terms of dominance and extended dominance.

Table 6 Base-case results (deterministic) – B.3.7 (p 132)

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
MF -> MF	£5,763	23.039	15.8510	..	..	..		..
MF -> Spherox	£7,156	23.039	15.8514					Ext. Dominated
MF -> ChondroCelect	£8,168	23.039	15.8492					Dominated
MF -> MACI	£8,168	23.039	15.8490					Dominated
Spherox -> MF	£14,182	23.039	17.9711	£8,419	0.000	2.1201		£3,971
Spherox -> Spherox	£15,017	23.039	17.9717					Ext. Dominated
MACI -> MF	£20,544	23.039	18.1168	£6,362	0.000	0.1457		£43,676
ChondroCelect -> MF	£20,588	23.039	18.1101					Dominated
MACI -> MACI	£22,091	23.039	18.1157					Dominated
ChondroCelect -> ChondroCelect	£22,283	23.039	18.1090					Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.14 Probabilistic sensitivity analysis

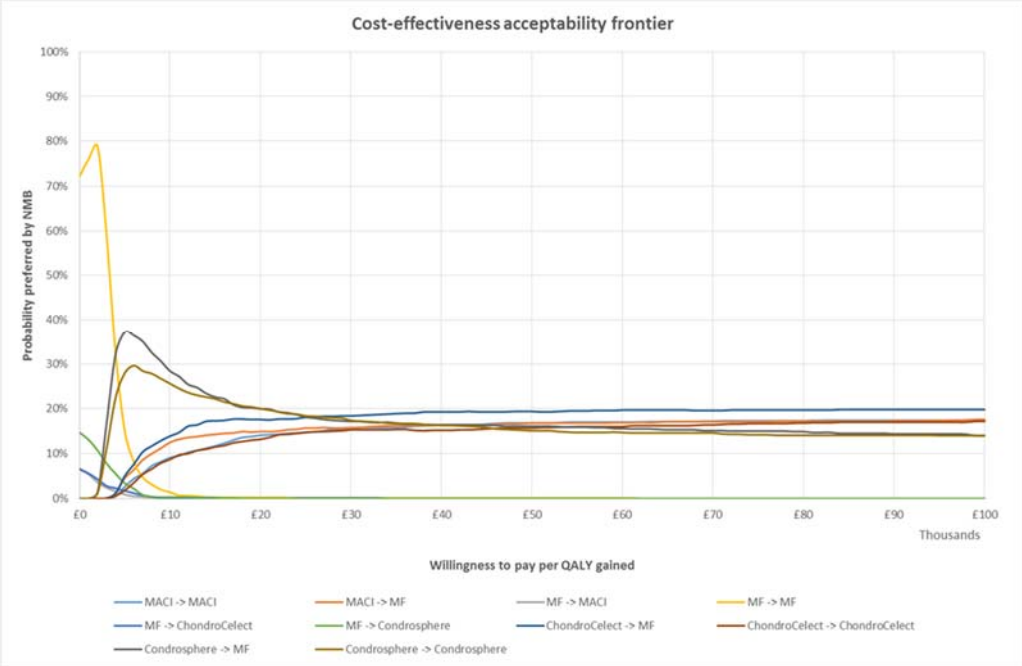
The results of the PSA are presented in terms of net monetary benefit (NMB) at a WTP threshold of £20,000 per QALY.

The tabulated PSA results (**Table 7**) give the probability (%) of each treatment pathway being preferred by NMB at WTP of £20,000. The results show that Spherox followed by MF and Spherox followed by Spherox have the highest probability (each 20%). The CEAF (**Figure 2**) gives a graphical representation of the probability of being preferred by NMB for all comparators at varying WTP thresholds up to £100,000. At the £20,000 threshold on the X-axis, Spherox followed by MF and Spherox followed by Spherox are shown at 20% probability (Y-axis).

Table 7 Base-case results (probabilistic) – B.3.8 (page 139)

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	Preferred NMB
MF -> MF	£5,572	15.8364	..	..	..	0.2%
MF -> Spherox	£6,848	15.8458			Ext. Dominated	0.0%
MF -> MACI	£7,811	15.8355			Dominated	0.0%
MF -> ChondroCelect	£7,848	15.8374			Dominated	0.0%
Spherox -> MF	£14,041	17.9756	£8,469	2.1392	£3,959	20.0%
Spherox -> Spherox	£14,698	17.9905			Ext. Dominated	20.0%
MACI -> MF	£20,389	18.1668	£6,348	0.1912	£33,206	14.9%
ChondroCelect -> MF	£20,451	18.1509			Dominated	17.6%
MACI -> MACI	£21,655	18.1694	£1,266	0.0027	£476,769	14.1%
ChondroCelect -> ChondroCelect	£22,006	18.1407			Dominated	13.2%
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Figure 2 Cost effectiveness acceptability frontier – B.3.8 (page 140)



A.15 Key sensitivity and scenario analyses

The deterministic sensitivity analysis (DSA) was performed on Spherox followed by MF versus MF followed by MF. Parameter values were varied by 20%.

The DSA is presented in terms of net monetary benefit (NMB) at a WTP threshold of £20,000 per QALY. – the most significant drivers are listed from top to bottom.

Figure 3 Tornado diagram: Spherox followed by MF vs. MF followed by MF – B.3.8 (page 144)

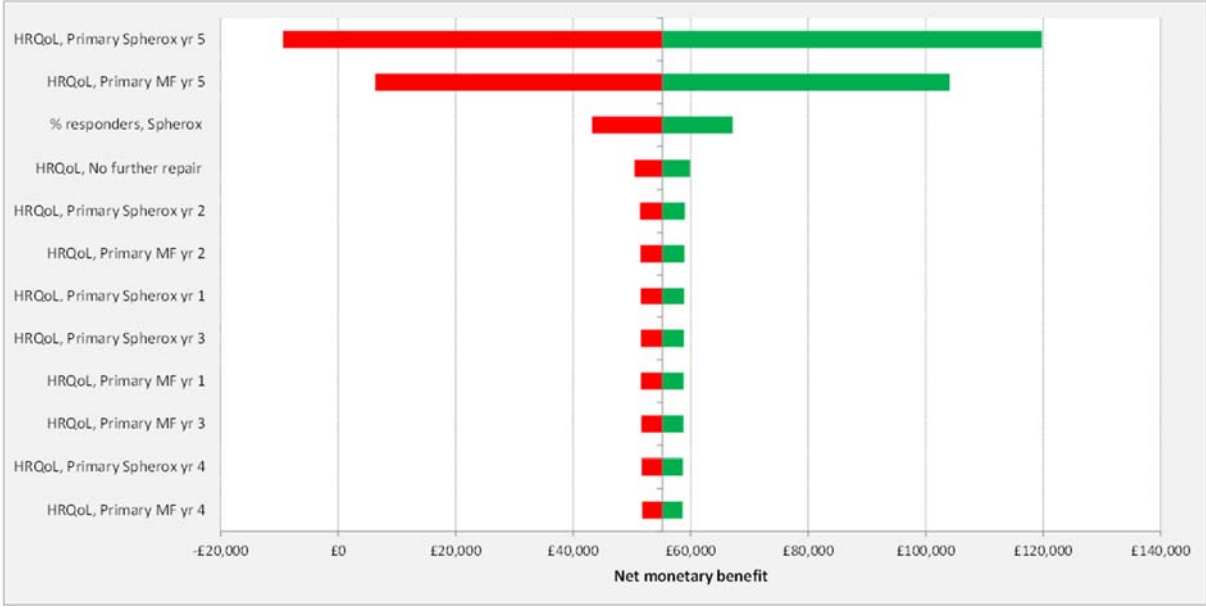


Table 8 Key scenario analyses - Spherox followed by MF vs. MF followed by MF (B.3.8 PAGE 145-150)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			£3,971
Shorter time horizon B3.8 (p 145)	Time horizon: 5 year	Explore impact on results of the timing of costs and benefits	Spherox -> MF: £75,395 [+£71,424]
Shorter time horizon B3.8 (p 145)	Time horizon: 15 year	Explore impact on results of the timing of costs and benefits	Spherox -> MF: £8,497 [+£4,526]
Shorter time horizon B3.8 (p 145)	Time horizon: 25 year	Explore impact on results of the timing of costs and benefits	Spherox -> MF: £5,404 [+£1,433]
Varying utilities	Changing Year 5+ Utility for MF	Explore sensitivity of results to this assumption	Spherox -> MF: £94,383 [+£90,412]
Equivalence efficacy between Spherox and MF	Failure rate equal between Spherox and MF	Results obtained from the indirect comparison were not statistically significant	Spherox -> MF: £4,061 [+£90]

A.16 Innovation (Document B, B.2, B.2.12, p90-91)

Spherox is a fourth generation ACI and represents a marked improvement over micro fracture (MF) and the other ACIs available. Using Spherox as first line surgical treatment before MF could be more effective than using MF first line before Spherox. Spherox aims to produce hyaline-like cartilage whereas MF is associated with the production of fibrocartilage which is inferior. It also is more effective than MF across age categories studied and can be used for large defects (up to 10 cm2) whereas MF is generally used on smaller defects (1-4cm2). Spherox may reduce the chances of rejection and incompatibilities as well as viral contaminations because of the autologous cells used in the procedure. It also overcomes any objections to the procedure on religious grounds, as the collagen membrane is not porcine derived.

Spherox is a 4th generation autologous product whereas traditional ACIs are 3rd generation. Spherox treatment application is less invasive than other ACIs, resulting in lower healthcare resource utilization and providing similar or greater health benefits at a lower cost than other ACIs. Unlike other ACIs, Spherox is 100% autologous and additive free (Document B, B.1, B.1.3, 18). In addition Spherox costs less than other ACIs (MACI and ChondroCelect).

For further information see the section on innovation in the main submission: B.2.12 (page 90-91).

A.17 Budget impact

A detailed description of the assumption and methods used to conduct the budget impact analysis can be found in the company budget impact analysis submission document (sections 3 (eligible population), 4 (resource use), 5 (uptake and market share). Detailed results can be found in the same document ((sections 6 (Benefits and savings), 7 (estimated annual budget impact)).

Table 9 Budget impact – Company budget impact analysis submission (page 10)

	Company estimate	Cross reference
Number of people in England who would have treatment	500 people are estimated to be eligible for primary repair with ACI each year in the UK	(Company budget impact analysis submission, 3 (page 6-7)
Average treatment cost per person	£11,467.94	(Company budget impact analysis submission, 4, table 4 (page 8)
Estimated annual budget impact on the NHS in England	Year 1: £217,697 Year 2: £1,097,192 Year 3: £1,990,745 Year 4: £2,898,524 Year 5: £3,595,954 Cumulative at year 5: 9,800,112	(Company budget impact analysis submission, 7, table 8 (page 10)

A.18 Interpretation and conclusions of the evidence

Phase III trial data shows that Spherox was at least as effective as that of the microfracture treatment across all criteria, and for some efficacy measures was better. In the first year after treatment, patients in the Spherox group improved more quickly than those in the microfracture group. A greater improvement was seen in the microfracture group during the second year. The primary statistical analysis at 12 and 24 months after treatment confirmed the non-inferiority of Spherox compared with microfracture. The two treatments had largely similar adverse event profiles. No unwanted effects of the study treatment were observed during examinations of other safety variables during the study.

An indirect comparison found that, compared with other ACIs, there are no statistically significant differences versus Spherox and so these treatments could be considered of similar efficacy. However, the results from the indirect comparison should be interpreted with caution given the high level of heterogeneity across the trials included.

Results of the economic analysis show that Spherox followed by microfracture is the cost effective strategy either amongst only microfracture sequences or including other ACI sequences. Compared with microfracture sequences, Spherox results in a greater number of QALYs (17.97 vs. 15.85 per patient) and costs (£14-15,000 vs. £5-7,000), producing an overall cost per QALY gained of £3,971 for Spherox followed by microfracture vs. microfracture followed by microfracture.

Overall, the cost effectiveness analysis developed for this submission shows that Spherox is a cost effective use of NHS resources compared with either microfracture or other ACIs, based on current list prices for all comparators. Most scenario or sensitivity analyses show that this conclusion is robust to changes in the assumptions and data used in the model.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
Spherox_ID581_DocumentB_18DEC17_redacted	1.0	No	18 DECEMBER 2017

Contents

Abbreviation

ARI	Aberdeen Royal Infirmary
ADL	Active daily living
Aes	Adverse events
ANCOVA	Analysis of covariance
KACI	Autologous chondrocyte implantation
AVN	Avascular Necrosis
BSC	Best supportive care
BMI	Body mass index
CrI	Credible Interval
CL	Confidence limit
DSU	Decision Support Unit
EED	Economic Evaluation Database
eCRF	Electronic case report form
EDC	Electronic data-capture
ePRO	Electronically recorded patient-reported outcome
EMA	European Medicines Agency
EPAR	European public assessment report
ECM	Extracellular matrix
FA	Final assessment
GCP	Good Clinical Practice
HRQoL	Health-related quality of life
HS	Health state
HPC	Hepatitis C
HCHS	Hospital and Community Health Services index inflation indices
HIV	Human immunodeficiency virus
hMSC	Human mesenchymal stem cells
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KOOS	Knee Injury and Osteoarthritis Outcome Score
KR	Knee replacement
LOCF	Last Observation Carried Forward
LYG	Life years gained
MRI	Magnetic resonance imaging
MOCART	Magnetic resonance observation of cartilage repair tissue
MACI	Matrix-applied characterized autologous cultured chondrocytes
ACI-M	Matrix-associated ACI
MA	Marketing authorisation
MF	Microfracture
Mon	Monitoring
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSAID	None-steroids anti-inflammatory drug

n_P	Numbers of patients
n_E	Number of events
OWSA	One way sensitivity analysis
OATS	Osteoarticular Transfer System
OA	Osteoarthritis
OAT	Osteochondral Autograft Transplantation
OC allograft	Osteochondral allograft
OCD	Osteochondritis dissecans
PKR	Partial knee replacement
PPAC	Per-patient average charge
PP	Per protocol
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized clinical trial
n_C	Recorded conditions
RR	Relative risk
RNOH	Royal National Orthopaedic Hospital
SAEs	Severe adverse events
Sport/Rec	Sport and recreation
SmPC	Summary of product characteristics
SOC	System Organ Class level of MedDRA
Tech	Technology
TA	Technology Appraisal
3D	Three-dimensional
TKR	Total knee replacement
Treat	Treatment
WTP	Willingness-to-pay
WORMS	Whole Organ MRI Score

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

The technology is Spherox, a 4th generation autologous chondrocyte implantation (ACI) technique licenced for 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. The treatment of defect sizes up to 10 cm^2 is eligible for single as well as adjacent defects (combined area) (1).

The decision problem is summarised in Table 1 below.

The population considered in the decision problem is adults with articular cartilage defects, in line with the final scope.

The comparators considered in the decision problem are microfracture (MF) and other ACIs (MACI and ChondroCelect), which were included in the final scope. Other comparators included in the scope issued by NICE were considered not relevant for the target population or not currently used in the UK.

The outcomes of the decision problem are the same as the final scope except for the exclusion of adverse events, which were not considered.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with articular cartilage defects	Adults with articular cartilage defects	N/A
Intervention	Spherox	Spherox	N/A
Comparator(s)	Microfracture (marrow stimulation) ACI (subject to ongoing NICE appraisal) Knee lavage and debridement Mosaicplasty Osteotomy (realignment of the knee) Best supportive care (non-operative intervention)	Microfracture ACI (MACI and ChondroCelect)	Some of the initially stated comparators were considered not relevant for the target population or not currently used in the UK
Outcomes	Pain, knee function including long-term function, rates of re-treatment, activity levels, avoidance of osteoarthritis including knee replacement, adverse effects of treatment, health-related quality of life	Pain, knee function including long-term function, rates of re-treatment, activity levels, avoidance of osteoarthritis including knee replacement (incorporated into economic modelling only), health-related quality of life	N/A

B.1.2 Description of the technology being appraised

Spherox is a new 4th generation ACI, which develops the cartilage *in vitro*. Cultured chondrocytes are seeded into agarose to form stable chondrocyte aggregates (spheroids). These spheroids, or "microtissues", are induced to form cartilage-like tissue and are grown *in vitro* for 6 to 8 weeks. The resultant spheroids are then transplanted into the defect (1).

The European Medicines Agency (EMA) granted marketing authorisation for Spherox on 10th July 2017. The approved indication comprises the repair of symptomatic articular cartilage International Cartilage Repair Society (ICRS) grade III or IV defects on the femoral condyle and on the knee patella, for defects of up to 10 cm^2 in adults. It has been studied in trials in adults with cartilage defects of knee and other joints but only those studies involving knee cartilage defects are reported in this submission (1).

Table 2: Technology being appraised

UK approved name and brand name	Spherox
Mechanism of action	The mode of action of Spherox is based on the removal of the patient's own chondrocytes isolated from healthy cartilage, their culture in vitro and their subsequent implantation into the cartilage defect. Spherox is cultured and implanted as three-dimensional spheroids. Spherox uses a technique in which the cartilage is developed *in vitro*. Cultured chondrocytes are seeded into agarose to form stable chondrocyte aggregates (spheroids). These spheroids, or "microtissues" are induced to form hyaline like cartilage tissue and are grown in vitro for 6 to 8 weeks. The resultant spheroids are then transplanted into the defect.
Marketing authorisation/CE mark status	The European Medicines Agency (EMA) granted Spherox marketing authorisation on 10 July 2017. The approved indication is for 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. The treatment of defect sizes up to 10 cm^2 is eligible for single as well as adjacent defects (combined area). CO.DON AG develops, produces, and markets autologous cell therapies for the minimally invasive repair of cartilage damage to joints following traumatic or degenerative defects. Spherox is a cell therapy product that uses only the patient's own cartilage cells ("autologous chondrocytes") and has been approved

	by the German federal agency PEI in accordance with Section 4b of the German Pharmaceuticals Act (AMG). The technology, marketed under the name co.don chondrosphere, has been used for more than 10 years in over 120 clinics to treat more than 11,000 patients.
Indications and any restriction(s) as described in the summary of product characteristics (1)	The approved indication is for 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. The treatment of defect sizes up to 10 cm^2 is eligible for single as well as adjacent defects (combined area). Spherox is an autologous product and should not be given to any other patient than the donor. Spherox is not recommended in children or adolescents below 18 years. Spherox is not recommended for pregnant or breast-feeding women. *Contraindications* • Patients with not fully closed epiphyseal growth plate in the affected joint. • Primary (generalised) osteoarthritis. • Advanced osteoarthritis of the affected joint (exceeding grade II according to Kellgren and • Lawrence). • Infection with the hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV I/II viruses.
Method of administration and dosage	Spherox is intended exclusive for use in a matrix-associated ACI (ACI-M). The implantation must be performed during a surgical procedure (preferably an arthroscopy or mini-arthrotomy). A debridement of the defect area is required. The subchondral plate should not be damaged. The spheroids are provided in a pre-filled syringe or an applicator (stem length 150 mm or 250 mm, co.fix® 150 or 250, respectively). Spheroids should be applied evenly on the defect ground and, if necessary, spread over the whole defect area by means of surgical instruments. The spheroids self-adhere within 20 minutes onto the defect ground. Afterwards, the surgical wound can be closed without any additional cover, e.g., periosteal flap of the treated area, or any fixation of spheroids by using fibrin glue. Patients treated with Spherox have to undergo a specific rehabilitation program. The program may take up to one year, depending on the recommendation of the physician. *Posology* 10–70 spheroids are applied per square centimetre defect.

Additional tests or investigations	*General*: Spherox is an autologous product and should not be given to any other patient than the donor. Prior to use, verify if the patients name matches the information of the patient/donor provided on the shipping documents and the product label. Also check if the correct order number (lot number) is on the primary package. If the primary or secondary packaging is damaged and therefore unsterile, Spherox should not be applied. *Paediatric population*: Before a cartilage defect in an adolescent patient is treated it has to be radiologically confirmed that the epiphyseal growth plate is closed. *Precautions for use*: Patients with local inflammations or acute as well as recent bone or joint infections should be deferred until the recovery from the infection. If possible, concomitant joint diseases should be corrected prior to or at the latest, at the time of Spherox implantation *Rehabilitation*: After implantation, the patient should follow an appropriate rehabilitation schedule. Physical activity should be resumed as recommended by the physician. Too early and vigorous activity may compromise the grafting and the durability of clinical benefit from Spherox.
List price and average cost of a course of treatment	£10,000
Patient access scheme (if applicable)	Previously, a confidential price of [redacted] was agreed with the Department of Health but this was specifically for an early access scheme and only relates to unlicensed co.don chondrosphere.

B.1.3 Health condition and position of the technology in the treatment pathway

Overview

Articular cartilage provides a smooth, lubricated surface for articulation at synovial joints. It is a specialized connective tissue that comprises hyaline and that lacks blood vessels, lymphatics, and nerves. Articular hyaline cartilage is 2 to 4-mm thick and is composed of a dense extracellular matrix (ECM) with a sparse distribution of chondrocytes – specialized cells involved in the development, maintenance, and repair of the ECM (2).

Articular cartilage injuries are precursors to long-term musculoskeletal morbidity, particularly as cartilage has a limited capacity for healing and repair. Consequently, treatment and repair or restoration of articular cartilage are challenging for the patient, the surgeon, and the physical therapist (2).

Articular cartilage defects can be caused by injury (often sports related), or wear and tear leading to osteoarthritis. Cartilage damage may also arise because of knee instability or abnormal unbalanced pressures, for example after an injury to a ligament or meniscal cartilage causing wear and tear on joints. Obesity may also cause osteoarthritis in knee cartilage and hip damage due to excessive weight-bearing (3). Condylar or patellar defects often become symptomatic and if they persist progress to secondary osteoarthritis, which affects daily living activities and quality of life (4).

The precise prevalence of symptomatic articular cartilage defects in the UK is unknown due to a lack of reliable estimates. However, every year in the UK it is thought that approximately 10,000 people require treatment for cartilage damage. Of these, it is projected that 200 and 500 people each year have symptomatic cartilage defects suitable for ACI (5).

Treatment pathway

In the UK, patients with symptomatic articular cartilage defects in the knee will first be offered best supportive care (BSC) before surgical interventions. BSC options include, but are not limited to, weight loss, physiotherapy, corticosteroid injections, and pain medication (6). If symptoms persist, the patient will be considered for

reparative/restorative procedures which may include knee lavage (with or without debridement, the removal of damaged cartilage), microfracture (MF), mosaicplasty, and autologous chondrocyte implantation (ACI). Osteotomy (realigning of the knee) and knee replacement are surgical options reserved for larger lesions and those where cartilage repair has failed (7). In the UK, the main options currently are MF, mosaicplasty and ACI; the selection of the procedure depends on a range of patient-related factors (history of surgery, age, BMI) and condition of the damaged cartilage (including lesion size). ACI is the preferred choice in UK clinical practice (8), however, due to access issues MF is the most common procedure performed. If symptoms persist after MF or ACI, other interventions will be considered, including mosaicplasty or ACI. MF would not be preferred as a second intervention if MF was previously performed. Knee replacement (total and partial) are only considered as the last treatment option in UK clinical practice if osteoarthritis develops (6).

Neither MF nor mosaicplasty have been appraised by NICE through the single or multiple technology appraisal process. Interventional Procedure Guidance (IPG 162) (9) does exist for mosaicplasty and recommends that it should only be used with special arrangements for clinical governance, consent, and audit or research.

Following a technology appraisal of ACI in 2005, NICE did not recommend ACI for the treatment of articular cartilage defects of the knee except in the context of ongoing or new clinical studies [TA89] (10), however new NICE guidance, expected to be published September 2017, based on a recent multiple technology appraisal of ACIs is expected to reverse this recommendation (11). The new decision is that ACI is recommended for first line surgical treatment following BSC, provided the following conditions are met (6):

- The patient has not had previous knee repair surgery;
- The patient has minimal osteoarthritic damage;
- The defect size is greater than 2 cm^2; and
- The procedure was performed at a tertiary referral centre.

The appraisal committee acknowledged in their final determination that a consensus of 104 UK clinical experts considered ACI as the only effective option for treating

defects greater than 2 cm^2 when symptoms persist following non-surgical management (6, 8).

Autologous chondrocyte implantation was first performed 20 years ago and comprises a series of procedures. First, chondrocytes are harvested arthroscopically from the affected knee joint. The cells are cultured in a laboratory for 8 weeks and then the cells are implanted into the damaged areas of the cartilage during a second surgical procedure (12). The advantage of ACI is that hyaline-like cartilage develops in the defect, rather than fibrocartilage when MF for example is performed, which may result in improved durability of the healing tissue and better long-term outcomes. Use of synthetic scaffolds is a potentially attractive alternative to traditional cartilage procedures as they are readily available and, unlike allogeneic tissue transplants, are associated with no risk of disease transmission (13).

Spherox is a new 4th-generation ACI that received EMA marketing authorization on 10 July 2017. Spherox treatment application is less invasive than other ACIs, resulting in lower healthcare resource utilization and providing similar or greater health benefits at a lower cost than other ACIs or ACI technologies. Unlike other ACIs, Spherox is 100% autologous and additive free (14). Spherox was not appraised in the NICE Multiple Technology Appraisal: ACI for repairing symptomatic articular cartilage defects of the knee (TA89) (10). This Company Evidence Submission relates to a Single Technology Appraisal.

B.1.4 Equality considerations

Spherox contains no animal derivatives nor any additional delivery mechanisms (e.g., scaffolds) of animal origin. Therefore, there is no patient exclusion based on ethical, moral, or religious grounds.

<u>Paediatric population</u> (15)

In concordance with the PIP (EMEA-001264-PIP01-12), a prospective non-interventional investigation (cod 16 HS17 paed) was initiated to evaluate the long-term safety and efficacy of the ACT3D product in adolescents from 15 to 17 years of age (inclusive) treated with the commercial product up to December 2011. Data are available from an interim analysis (cut-off date 31.01.2016).

Two studies, cod 16 HS 16 (2012) and cod 16 HS 17 paed (2016), have demonstrated that ACT3D using Spherox was considered suitable, safe and effective for the treatment of cartilage defects of the knee in adolescents of 14 to 17 years of age. In total, 58 adolescents were investigated in both studies. An overlap of 12 patients between cod 16 HS16 and cod 16 HS17 paed were found.

Older people (15)

In clinical practice, patients up to 55 years of age have usually been treated. Clinical data of adult patients aged over 55 years are limited. The application of Spherox in patients older than 50 years has not been studied. Applying Spherox to older patients with advanced cartilage degeneration or osteoarthritis is not recommended.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Two RCTs (Phase II and Phase III) were identified from the literature search (described in Appendix D) as relevant to the technology being appraised. In addition, there is a summary of 12 non-RCT studies of Spherox in **Error! Reference source not found.**. Only the Phase III trial has been used in the cost effectiveness model.

B.2.2 List of relevant clinical effectiveness evidence

This submission is based on a prospective, randomised, open label, multicentre Phase III clinical trial designed to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product Spherox with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm^2 (15). In addition, the phase II trial for the same technology, defect sizes between 4 and 10 cm^2, has been summarised in order to provide a complete overview of the clinical trial program in patients with knee cartilage defects (16).

Table 3: Clinical effectiveness evidence of Phase III trial

Study	NCT01222559 (COWISI)				
Study design	Prospective, randomised, open label, multicentre Phase III clinical trial				
Population	The analysis population comprised 102 patients (41 women, 61 men) aged 37 ± 9 years.				
Intervention(s)	Implantation of three-dimensional autologous chondrocyte implantation product (Spherox) into the cartilage defect, resulting in hyaline cartilage repair. There are two study interventions: a single arthroscopy including harvesting of chondrocytes and, after approximately 2 months, a single implantation of the study product Spherox.				
Comparator(s)	Marrow-stimulating method (microfracture)				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	This study was a comparative analysis in the relevant population and against appropriate comparator.				
Reported outcomes specified in the decision problem	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from Day 0 (baseline for both treatment groups = pre arthroscopy assessment) to final assessment (FA) 24 months after the end of the respective treatment, compared between the two study treatment groups (Spherox and microfracture). The 36-, 48- and 60-month visits are follow-up visits. Overall KOOS including 5 Subscores (Pain, Knee function including long-term function, activities of daily living, other				

Study	NCT01222559 (COWISI)
	symptoms and quality of life). Activity levels, avoidance of osteoarthritis including knee replacement, adverse effects of treatment, health-related quality of life
All other reported outcomes	MOCART (MRI Score), ICRS and ICRS II Visual Histological Assessment Score, Bern Score, Change of ICRS/IKDC, Change of modified Lysholm Score Days of absence from work

Table 4: Clinical effectiveness evidence of Phase II trial

Study	Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm2) with 3 different doses of the autologous chondrocyte implantation product Spherox in subjects with cartilage defects of the knee (Trial no. cod 16 HS 14)				
Study design	Prospective, phase II, multicentre, randomised, open label (central radiologist as blind observer for MRI), dose-response study.				
Population	Male and female patients between ages of 18 and 50 years with an isolated single cartilage defect of the knee joint				
Intervention(s)	Product ACT3D-CS = autologous chondrocyte product Spherox Group A: ACT3D-CS in patients receiving 3-7 spheroids/cm2 Group B: ACT3D-CS in patients receiving 10-30 spheroids/cm2 Group C: ACT3D-CS in patients receiving 40-70 spheroids/cm2				
Comparator(s)	Not applicable				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale for use/non-use in the model	Not used in the model as not comparison with microfracture that could be included in the network meta-analysis.				
Reported outcomes specified in the decision problem	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from baseline to final assessment at 12 months (after implantation). The 24, 36-, 48- and 60-month visits are follow-up visits.				
All other reported outcomes	• Related changes in KOOS • MOCART (magnetic resonance observation of cartilage repair tissue) • Modified Lysholm score • IKDC (International Knee Documentation Committee) knee examination form • IKDC current health assessment form • IKDC subjective knee evaluation form • Bern score • International Cartilage Repair Society rating				

Phase II trial (Trial no. cod 16 HS 14) was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study support the efficacy results of Spherox and offer long-term data (4 years) for efficacy and safety. This study was not included in the economic model because it is not comparative.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Phase III trial

Objective

The overall objective of this trial was the assessment of the long-term efficacy and safety of the three-dimensional autologous chondrocyte implantation product Spherox in comparison with microfracture for the treatment of cartilage defects of knee joints (15). The results presented in this submission are taken from the 24-month analysis of the trial. These results have yet to be published (15).

Trial design

This was a prospective, randomised, actively controlled, multicentre Phase III study with two parallel treatment arms. The trial was not blinded, however, MRI and re-biopsies were assessed centrally by blinded independent radiologists and pathologists, respectively.

Eligible patients who had signed informed consent forms underwent arthroscopy to assess the size of the cartilage defect and the ICRS grade for the final assessment of the patient's eligibility for enrolment (15). Randomisation was undertaken in the operating theatre during arthroscopy. Patients with a defect size of >1 cm^2 to <4 cm^2 after debridement were randomly allocated during arthroscopy to Group A or Group B in a 1:1 ratio.

Group A: Spherox

The pre-implantation phase was of approximately 3 months duration. There were two study interventions. At the initial arthroscopy, chondrocytes were harvested and, approximately 2 months later, the study product *Spherox* was implanted. For patients in Group A, the pre-treatment day was the day before the implantation procedure, termed as Day 0' .

Group B: Microfracture

The pre-operation phase was a maximum 1 month duration. Treatment consisted of a single intervention with arthroscopy and microfracture being conducted on the same day.

Patients were stratified into two age groups at randomisation (18–34 years old inclusive and >35 years old); there was no other stratification at recruitment.

The first study patient gave written informed consent to participate on 14 December 2010 and underwent screening on the same day. The last patient included in the present analysis attended for Visit 6 (the 12-month examination) on 20 February 2017 (15).

Selection of study population

Patients were selected for possible inclusion in the trial based on the following inclusion and exclusion criteria. These criteria align to the expected recommended population for ACIs (6).

Table 5. Eligibility criteria [(15), p52, sec9.3.1]

Inclusion criteria	Exclusion criteria
1. Male or female patients, aged ≥18 years and ≤50 years. 2. Defect: isolated ICRS grade III or IV single-defect chondral lesion on femoral condyle. 3. Defect size: ≥1 and <4 cm^2 after debridement to healthy cartilage, up to 6 mm in depth. Assessment with MRI at screening and by estimation during arthroscopy before randomisation. 4. Nearly intact chondral structure surrounding the defect as well as an intact corresponding joint area. 5. Informed consent signed and dated by the patient. 6. The patient understood the strict rehabilitation protocol and follow-up programme and was willing to follow it. 7. In case of pain, the patient agreed to use only paracetamol mono- (maximum 4 g/day) or a combination preparation and oral and/or topical NSAIDs during the trial, and to discontinue the use of oral and/or topical NSAIDs and/or paracetamol combination preparations 1 week before each visit (the use of paracetamol mono-preparations (maximum 4 g/day) was allowed). However, in the morning of the visit day, no pain medication was allowed. Other pain medications were allowed during surgical operation procedures and could be taken for a period not exceeding 4 weeks after surgery. (A list of NSAIDs was provided for reference in Appendix 3 of the study protocol.)	1. Defects in both knees at the same time. 2. Radiological signs of osteoarthritis. 3. Any signs of knee instability. 4. Osteochondritis dissecans (OCD) 5. Valgus or varus malalignment (more than 5° over the mechanical axis). 6. Clinically relevant second cartilage lesion on the same knee. 7. More than 50% resection of a meniscus in the affected knee or incomplete meniscal rim. 8. Rheumatoid arthritis, parainfectious or infectious arthritis, and condition after these diseases. 9. Pregnancy and planned pregnancy (no MRI possible). 10. Obesity (body mass index > 30 kg/m^2). 11. Uncontrolled diabetes mellitus. 12. Serious illness. 13. Poor general health, as judged by the physician. 14. Participation in concurrent clinical trials or previous trials within three months of screening. 15. Previous treatment with ACI in the affected knee. 16. Microfracture performed less than one year before screening in the affected knee. 17. Alcohol or drug (medication) abuse. 18. Meniscal implant in the affected knee. 19. Meniscal suture (in the affected knee) three months before baseline. 20. Mosaicplasty (osteoarticular implant system, OATS) in the affected knee. 21. Having received hyaluronic acid intra-articular injections in the affected knee within the three months before baseline. 22. Taking specific osteoarthritis drugs such as chondroitin sulphate, diacerein, *N*-glucosamine, piascledine, capsaicin within two weeks of baseline. 23. Corticosteroid treatment by intra-articular route within the month before baseline or systemic (all routes) corticosteroids within the two weeks before baseline. 24. Chronic use of anticoagulants. 25. Any concomitant painful or disabling disease of the spine, hips or lower limbs that would interfere with evaluation of the afflicted knee. 26. Any clinically significant or symptomatic vascular or neurological disorder of the lower extremities. 27. Any evidence of the following diseases in the affected knee: septic arthritis, inflammatory joint disease, recurrent episodes of pseudogout, Paget's disease of bone, ochronosis, acromegaly, haemochromatosis, Wilson's disease, primary osteochondromatosis, heritable disorders, collagen gene mutation. 28. Current diagnosis of osteomyelitis and/or infection with human immunodeficiency virus (HIV-1, -2) and/or with hepatitis C (HCV).

Settings and locations where the data were collected

This trial was conducted at eleven orthopaedic clinics in Germany and Poland (see table below). The study population is assumed to be generalisable to the United Kingdom (17).

Table 6. Phase III trial locations

Germany
Universitätsklinikum der Albert-Ludwig-Universität Freiburg, Department Othopädie und Traumatologie
Freiburg, Baden-Würrtemberg, Germany, 79106
Waldkrankenhaus "Rudolf Elle" GmbH Klinik für Orthopädie und Unfallchirurgie
Eisenberg, Tühringen, Germany, 07607
Gelenk-und Wirbelsäulenzentrum Steglitz
Berlin, Germany, 12163
St. Vinzenz-Hospital
Dinslaken, Germany, 46535
Orthopädische Klinik der Medizinischen Hochschule Hannover
Hannover, Germany, 30625
Lubinus Clinicum Kiel
Kiel, Germany, 24106
DRK Krankenhaus Luckenwalde
Luckenwalde, Germany, 14943
Orthopädisch-Unfallchirurgisches Zentrum
Mannheim, Germany, 68167
Poland
Uniwersytecki Szpital Kliniczny w Białymstoku
Białystok, Poland, 15-276
Wojewódzki Szpital Chirurgii Urazowej
Piekary Śląskie, Poland, 62
Centrum Medycyny Sportowej
Warszawa, Poland

Trial drugs and concomitant medications

Group A

The study treatment consisted of autologous chondrocyte implantation (ACI) spheroids (Spherox). Spherox falls within the definition of a tissue-engineered product as defined in Article 2(1) (b) of Regulation 1394/2007/EC for advanced therapies (15, 18). ACI is based on the arthroscopic harvesting of the patient's chondrocytes isolated from healthy cartilage (15). The chondrocytes are cultured *in vitro* to develop 3-dimensional spheroids (Spherox) which effect hyaline cartilage repair following implantation into the cartilage defect.

Spherox was administered at the dose level stipulated in the summary of product characteristics (10 to 70 spheroids/cm^2). The amount of Spherox sent for implantation was determined at the site of manufacture so the dose administered could not be influenced by the physician conducting the implantation (15).

Group B

Microfracture is a marrow-stimulating method in which holes are created in the subchondral bone plate at the bottom of the cartilage defect to allow the passage of bone marrow blood. This blood contains pluripotent stem cells (hMSC) that are able to differentiate mainly into fibrochondrocytes, resulting in fibrocartilage repair. Microfracture is a surgical procedure; no products were involved.

Concomitant medication and additional treatment(s)

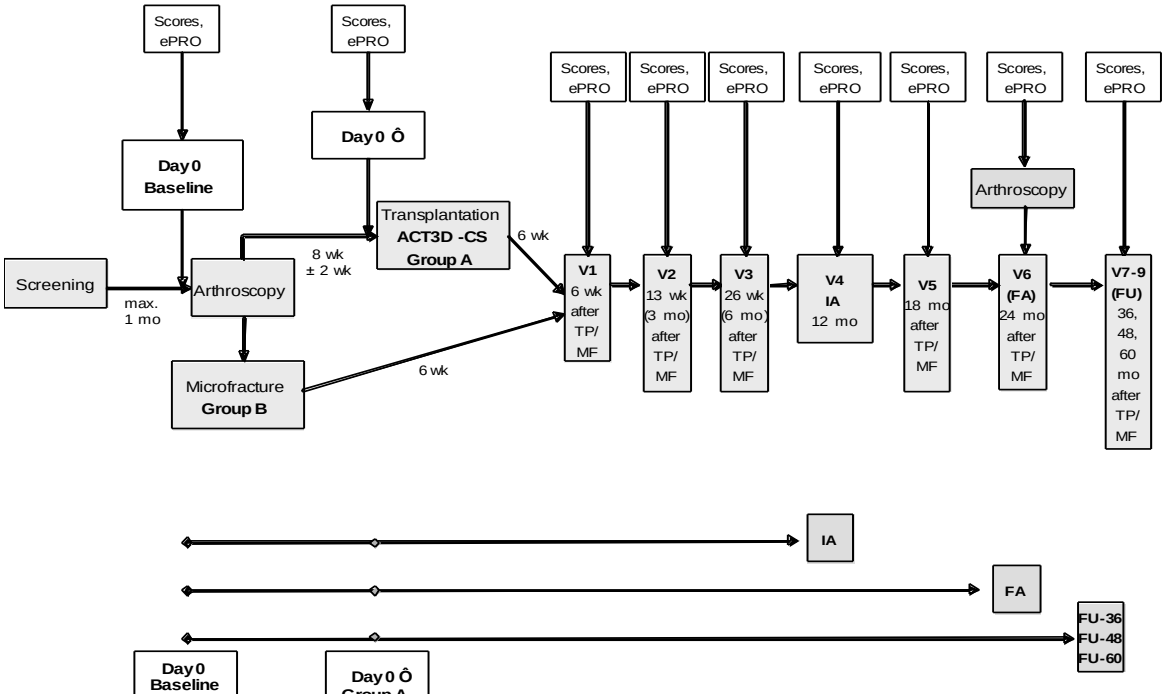
Illnesses present at the time of enrolment were considered "concomitant illnesses" and were treated with appropriate medications/measures if necessary. These and any other illnesses or surgical treatment of the patient and medications taken or measures performed during the six months before enrolment were documented in the electronic case report form (eCRF), Concomitant Illness & Medication/Measure Form.

Any medication/measure (including over-the-counter medication, multi-vitamin or nutritional supplements) taken by the patient or prescribed during the trial was also recorded in the Concomitant Illness & Medication/Measure Form (15).

Post-intervention assessments

Following the Spherox implantation (Group A) or microfracture (Group B) procedure, assessments were planned to be conducted at 6 weeks, 3, 6, 12, 18, 24, 36, 48, and 60 months. Completion of the 24-month visit by all patient triggered the final analysis. The 36-, 48-, and 60-month visits are follow-up visits; corresponding reports for the final and follow-up analyses are planned. A flow diagram presenting the course of the trial for each patient is shown in Figure 1. The assessment after 60 months (5-year follow-up) is defined as the end of the trial (15).

Figure 1: Study flow diagram [(15), p25, Figure1]



ePRO, electronically recorded patient-reported outcome; mo, months; wk, weeks; V, visit; TP, implantation; MF, microfracture; IA, interim analysis; FA, final analysis; FU, follow-up. For definitions of Day 0 and Day 0' see co.don AG CSR (15)]

Data management

Study investigators entered data into a central electronic database using a trial-specific eCRF, supported by a full electronic audit trail that recorded all changes to eCRF data. Patient-Reported Outcomes data were entered directly by the patients into an ePRO (electronic Patient-Reported Outcome) system specifically designed for the trial.

Clinical data were collected, collated and reviewed using an electronic data-capture system (EDC) designed specifically for the trial. Data management was performed by CSG using an ORACLE® data base (15).

Efficacy and safety measurements

Primary efficacy variable

Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from Day 0 (baseline for both treatment groups = pre-arthroscopy assessment) to final assessment (FA) 24 months after the end of the respective treatment, compared between the two study treatment groups (Spherox and microfracture) (15).

Secondary efficacy variables.

- Change of overall KOOS from baseline (Day 0) to 12 months (interim analysis) and 36, 48, and 60 months (follow-up, FU) after the end of the respective treatment, compared between the treatment groups.

- Change of overall KOOS from Day 0 for microfracture or from Day 0' for Spherox to 12, 24, 36, 48, and 60 months after the end of respective treatment.

- Change of the 5 subscores of the KOOS (pain, other symptoms, function in daily living [activities of daily living, ADL], function in sport and recreation (sport/rec), knee-related quality of life [QoL]) from baseline (Day 0 = pre-arthroscopy day) to 12, 24, 36, 48, and 60 months after the end of the respective treatment, compared between the treatment groups.

- MOCART (MRI Score) 12, 24, 36, 48, and 60 months after implantation or microfracture compared between the treatment groups.

- Arthroscopy and biopsy 24 months after implantation/microfracture, assessment of cartilage repair to be compared between the treatment groups.

- ICRS Visual Histological Assessment Score at final assessment (24 months) compared between the treatment groups.

- ICRS II Histological Score at final assessment (24 months) compared between the treatment groups.

- Bern Score and additional histological assessment scores at final assessment (24 months) compared between the treatment groups.

- Change of ICRS/IKDC from baseline (Day 0) to 12, 24, 36, 48, and 60 months after the end of the respective treatment, compared between the treatment groups.

- Change of modified Lysholm Score from baseline (Day 0) to 12, 24, 36, 48, and 60 months after the end of the respective treatment, compared between the treatment groups.

- Days of absence from work (employment) and/or days of inability to pursue usual activities during the last year or since the last study visit, respectively, and time point when patient was back at work and/or to could pursue usual activities (15).

Safety analyses

The frequency and type of adverse events, vital signs, physical examination, concomitant pain medication and laboratory values were analysed (15).

Baseline characteristics of the study population

Definition of baselines

Microfracture and Spherox differ in that with microfracture requiring one intervention while Spherox is a two-intervention method. As a consequence, “baseline” is established in slightly different ways for the two methods.

For both treatment groups, Day 0 is up to 10 days before the first arthroscopy. This first arthroscopy is identical to “study treatment” for the microfracture group as the bone-marrow stimulation procedure takes place during the arthroscopy. Therefore, Day 0 is defined as baseline.

However, the application of the product test Spherox takes place only two to three months after the first arthroscopy in patients randomised to the Spherox group. Therefore, in this group the baseline day (up to 10 days before) before implantation is termed Day 0' (15).

The study population

The study included 41 women (40%) and 61 men (60%). Basic demographic information about the patients are summarised in Table 7. The treatment groups were well balanced in respect of the patients' demographic details and disease background (Table 8). ICRS grades were evenly balanced between the groups; most were grade III B or IV A (Table 9) (15). Apart from minor imbalances in smoking habit (more smokers in the microfracture group), the key difference between the arms was in baseline KOOS scale (Spherox 56.6; MF 51.7).

Medical histories were similar in the groups. Although there were more reports of 'immune-system disorders' in the Spherox group it is unlikely that this difference affected the study result (Table 10) (15).

Table 7: Demographic data and baseline characteristics of the study patients (ITT/safety population) [(15), p85, Table9]

Characteristic	Spherox *N* = 52	Microfracture *N* = 50	All patients *N* = 102
Sex: female	19	22	41
male	33	28	61
Age [years]	36 ± 10	37 ± 9	37 ± 9
Height [cm]*	177 ± 9	175 ± 9	176 ± 9
Weight [kg]*	81.3 ± 15.4	79.7 ± 13.5	80.5 ± 14.4
BMI [kg/m^2]*	25.7 ± 3.3	25.8 ± 3.0	25.8 ± 3.1
range	18.8 – 31.2	18.2 – 30.0	18.2 – 31.2
Patient smoked: yes	14	20	34
no	38	30	68
Patient drank alcohol: yes	30	24	54
no	22	26	48
Pre-debridement defect size [cm^2]	2.2 ± 0.7	2.0 ± 0.8	2.1 ± 0.8
range †	0.5 – 3.5	0.8 – 4.0	0.5 – 4.0
Post-debridement defect size [cm^2]	2.7 ± 0.8	*not applicable*	*not applicable*
range †	1.4 – 5.0		
Defect location (primary) Femur	52	49	101
Tibia ‡	–	–	–
Patella	–	–	–
Femur and patella	–	1 §	1
Defect location (further defects <ICRS grade 3) Femur	–	–	–
Tibia	2	3	5
Patella	10	10	20

* Numbers of patients or mean ± SD, or where appropriate the range (minimum–maximum), are given.
† All values were within the allowed range (1–4 cm^2).
‡ This would have represented a violation of inclusion criterion no. 2 (Section 0). § Violation of inclusion criterion no. 2.

Table 8. Type of knee defect on day of arthroscopy (ITT/safety population) [(15), p85, Table10]

Diagnosis	Spherox *N* = 52	Microfracture *N* = 50	All patients *N* = 102
Traumatic cartilage lesion	19	24	43
Osteoarthritis	1	[redacted]	[redacted]
Avascular necrosis	–	1	1
Other	32	[redacted]	XX

Numbers of patients are given.

Table 9. ICRS grade of knee defects at baseline (day of arthroscopy; ITT1 population) [(15), p86, Table11]

ICRS grade	Spherox *N* = 48	Microfracture *N* = 49	All patients *N* = 97
III			
III A			
III B			
III C			
IV			
IV A			
IV B			
IV C			

Numbers of patients are given.

Table 10. Prior/concomitant illnesses at screening by MedDRA SOC and preferred term (ITT/safety population) [(15), p87, Table12]

Prior/concomitant illness	Spherox *N* = 52		Microfracture *N* = 50		All patients *N* = 102	
	n_P	n_C	n_P	n_C	n_P	n_C
Any SOC						
Immune-system disorders						
Drug hypersensitivity						
Seasonal allergy						
Food allergy						
House-dust allergy						
Allergy to chemicals						
Endocrine disorders						
Hypothyroidism						
Musculoskeletal and connective-tissue disorders						
Gastrointestinal disorders						
Gastro-oesophageal reflux disease						
Vascular disorders						
Hypertension						
Nervous system disorders						
Migraine						
Eye disorders						
Infections and infestations						
Metabolism and nutritional disorders						
Psychiatric disorders						
Renal and urinary disorders						
Respiratory, thoracic and mediastinal disorders						
Asthma						
Skin and subcutaneous disorders						
Investigations						

Cut-off: SOCs and preferred terms are shown that were mentioned for ≥3 patients under “All patients”.
Numbers of patients (n_P) and recorded conditions (n_C) are given.

B.2.3.2 Phase II trial

Trial design

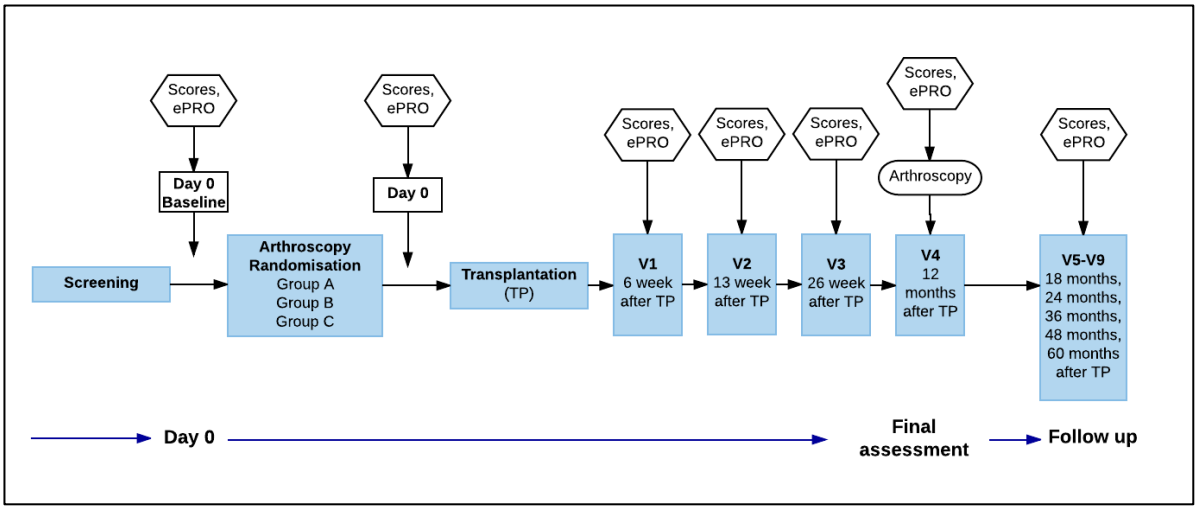
A multicentre, prospective, randomised, single-blind, phase II, dose-response study was designed to assess the short-term and long-term efficacy of three different doses of the three-dimensional autologous chondrocyte transplantation product Spherox for the treatment of cartilage defects (4-10 cm²) of knee joints.

Blood sampling and cartilage biopsy were performed for the preparation of autologous chondrocyte spheroids (Spherox) for subsequent implantation into the patient.

After screening and during arthroscopy, patients were prospectively stratified by the extent of the cartilage defect in the knee joint (4–7 or 7–10 cm^2) and, within each stratum, were randomised (1:1:1) to receive treatment with 3–7, 10–30 or 40–70 spheroids/cm^2. The trial was not blinded, but MRI images were assessed centrally by a blinded reader and histological assessments were made centrally by a blinded pathologist (16).

A summary of the course of the trial is shown as a study flow diagram in Figure 2.

Figure 2: Phase II trial design



Eligibility criteria

The main inclusion and exclusion criteria for patients to be enrolled in the study are listed in Table 11 below. Additional exclusion criteria (same as in the Phase III trial) were applied and can be found in Table 5.

Table 11: Phase II Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
18 – 50 years	Bilateral defects or two defects in the same knee
Defect size of 4–10 cm2	Radiological signs of osteoarthritis or knee instability
Isolated ICRS grade III or IV single defect on medial or lateral femoral condyle, trochlea, tibia and retropatellar defect, also osteochondritis dissecans (for osteochondritis dissecans, bone grafting up to the level of the original bone lamella was to be performed if bone loss exceeded 3 mm in depth)	Valgus or Varus misalignment >5°
Nearly intact chondral structure surrounding the defect and corresponding joint area	50% resection of a meniscus in the affected knee or incomplete meniscal rim; rheumatoid, parainfectious or infectious arthritis
Patients agreed to certain restrictions on pain medication, especially immediately before study visits	Obesity (body mass index > 30 kg/m^2)
Patients agreed to participate fully in the rehabilitation programme	Meniscal implant or recent suture in the affected knee

A total of 163 patients with unilateral knee defects were screened across the ten orthopaedic clinics between November 2010 and September 2012. 43 patients were excluded from enrolment due to the cartilage defect being too small. Another 45 failed to meet the other eligibility criteria listed. The remaining 75 patients were enrolled into the study and underwent biopsy to extract samples and culture the spheroids. In two patients who had already been randomised (to the low-dose and high dose-groups, respectively), the chondrocytes did not grow in the culture thus making implantation impossible. These two patients are not included in the intention-to-treat population (16).

Settings and locations

The study was based at ten orthopaedic clinics in Germany. The study population is assumed to be generalisable to the United Kingdom. Large differences are not expected in clinical practice between the two countries (16).

Trial drugs and concomitant medications

Enrolled patients were randomised (1:1:1) to receive treatment with 3–7, 10–30 or 40–70 ACI spheroids/cm^2. The standard Spherox treatment in clinical practice is 10–70 spheroids/cm^2, and this study was designed to compare three dose levels: two within the standard range (10–30 spheroids/cm^2 and 40–70 spheroids/cm^2) and one below it (3–7 spheroids/cm^2) in order to establish a minimum effective dose.

These ACI spheroids (Spherox) are cultured from samples taken from the patient (a biopsy is performed from the affected knee joint). The spheroids are induced to form cartilage-like tissue and are grown in vitro for 8 - 10 weeks and are then transplanted into the isolated cartilage defects of joints. The amount of spheroids was dependent on the treatment group the patient was randomised to (16).

Outcomes

The primary outcome reported in the dose-response trial was the Knee Injury and Osteoarthritis Outcome Score (KOOS) in the intention-to-treat population, which was pre-specified before analyses were run. The primary analysis was the overall change in KOOS at 12 months after implantation from the baseline value (Day 0). This was determined for each dosage group and between the dosage groups.

The KOOS is a 42-item, self-administered, self-explanatory questionnaire that covers five patient-relevant dimensions; pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QoL).

Standardised answer options were given (5 Likert boxes) to participants and each question received a score from 0 to 4. Scores were assigned as follows: none, 0; mild, 1; moderate, 2; severe, 3; extreme, 4. If one or two answers were missing, then the missing values were replaced with the average value for that subscale. A normalised

score (100 indicating no symptoms and 0 indicating extreme symptoms) was calculated for each subscale. The result can be plotted as an outcome profile.

The total score of each subscale was summed and divided by the possible maximum score for the scale. Traditionally in orthopaedics, 100 indicates no problems and 0 indicates extreme problems. The normalised score was therefore transformed to meet this standard. The overall KOOS score was determined by averaging the transformed subscores.

Following baseline, the KOOS were recorded for patients at 6 weeks following implantation, 13 weeks (3 months), 26 weeks (6 months), and the final assessment after 12 months. Additional follow-up assessments have taken place after 18 months, 24 months, 36 months and 48 months and the final assessment will be at 60 months following implantation (16).

The baseline characteristics are summarised in Table 12.

Table 12: Baseline characteristics of participants across dose groups

Baseline characteristics					
Dose group [spheroids/cm^2]		**Low 3 – 7 (N=25)**	**Medium 10 – 30 (N=25)**	**High 40 – 70 (N=25)**	**All patients (N=75)**
Sex	Female				
	Male				
Age [years]					
Height [cm]	Female				
	Male				
Weight [kg]	Female				
	Male				
BMI					
Smokes cigarettes	Yes				
	No				
Drinks alcohol	Yes				
	No				
Defect size at arthroscopy [cm^2]					
Defect size at implantation [cm^2]					
Defect size group	4-6.99 cm^2				
	7-10 cm^2				
Defect location (primary)	Femur				
	Tibia				
	Patella				
Defect location (further defects < ICRS grade 3)	Femur				
	Tibia				
	Patella				

Numbers of patients or mean ± SD, are given

The study population comprised 75 patients (22 women, 53 men) aged 34 ± 9 years. The three dose groups were well balanced in respect of age, height, weight, BMI and alcohol consumption. All but two of the study patients were Caucasian (73 patients, 97%); the other two were recorded as respectively Asian and Black.

The study population comprised 22 women (29%) and 53 men (71%) and there was an imbalance regarding sex between the dose-groups, with approximately 33% female patients in the low-dose group, 40% in the high-dose group and less than 20% in the medium-dose group. There was also a slight imbalance in respect of smoking, with a greater proportion of smokers in the low-dose group (32%) than in the other two groups (16% and 24%).

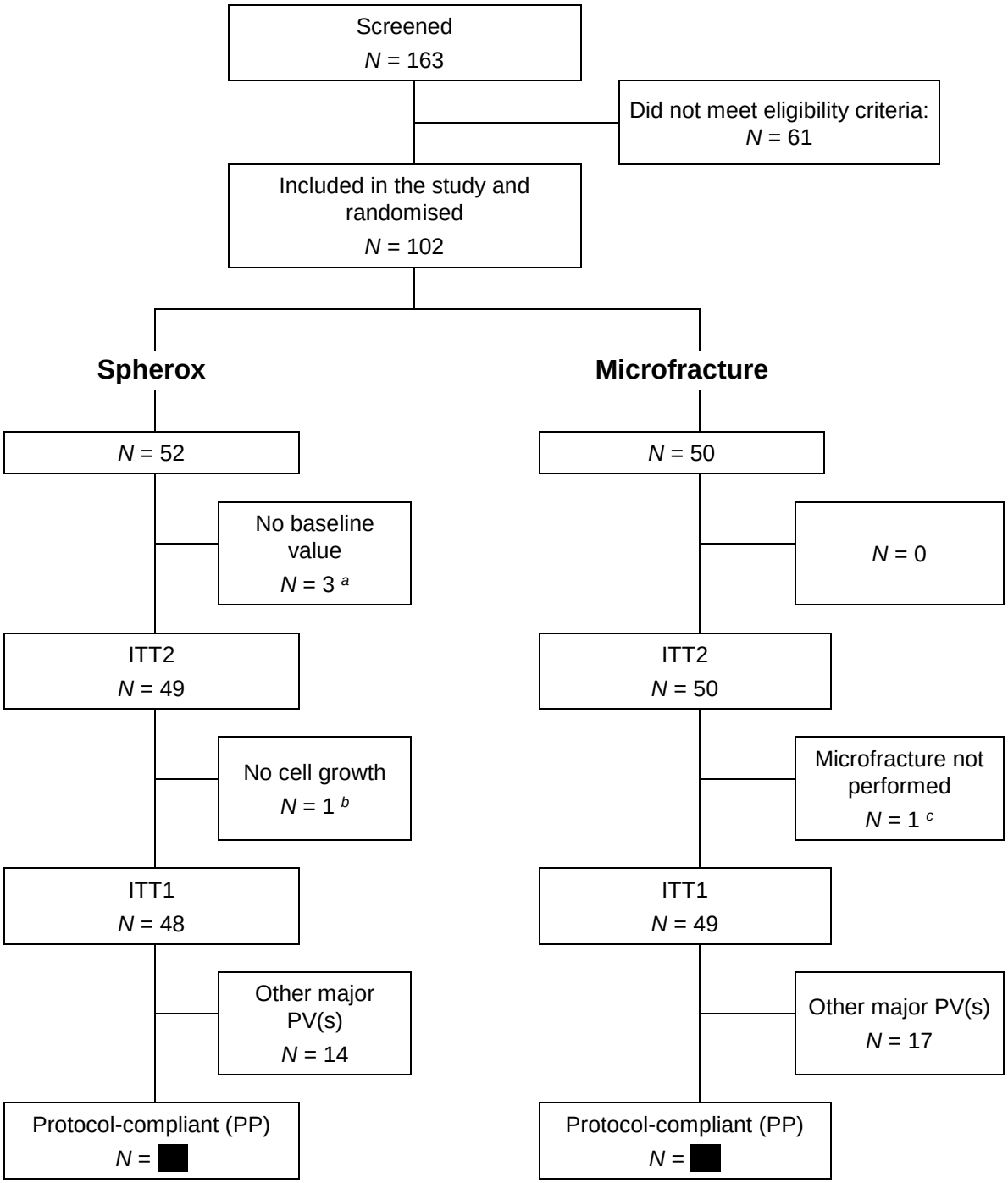
Primary cartilage defects were mostly (47/75; 63%) of the patella, the rest (28/75; 37%) being of the femur; no primary defect was of the tibia (16).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Phase III trial

Of the 163 patients screened for participation in the trial, 102 patients were eligible for inclusion. Fifty-two patients (51%) were randomised to the Spherox group and 50 patients (49%) to the microfracture group, three patients in the ACI group did not evaluate the baseline score and furthermore one patient in each group was not treated. This results in an ITT population of 48 patients in the Spherox group and 49 patients in the microfracture group. A summary of the recruitment and randomisation is given as a CONSORT flow chart (Figure 3) (15).

Figure 3: Patient disposition



PV, protocol violation. *a*, patients 2430, 2433 and 2710; *b*, patient 2289; *c*, patient 2278.

Sources: For screening, study data base; for patients in 24-month analysis, Tables 14.1.3 and 14.1.4.10.

Sample size calculation

The sample-size calculation considered the standardised KOOS in the range 0–100. The test of non-inferiority (Step 2; see 'data set analysis section' below) to compare Spherox with microfracture is the size-limiting step. The power for Step 1 results from the recommended sample size calculated for Step 2 (15).

Assumptions (percentages are absolute differences, i.e., percentage points):

- Test for non-inferiority with respect to overall KOOS
- α = 0.025 (one-sided)
- Power = 80%
- Definition from a clinical point of view which differences between Spherox and microfracture can be accepted as equivalent:
    - *Lower equivalence bound* = -8.5% caused by the assumption that equivalent clinical findings could differ in individual score items as follows: about 1/3 of the questions differ about one level between 0 to 4, in the other 2/3 of questions there is no difference considered over the scale 0–100 (15).
    - *Upper equivalence bound:* Does not apply.

Table 13 presents scenarios (nominal power = 80%), derived from the overall KOOS scoring manual as well as the paper by Saris *et al 2008 (19)*.

Table 13: Statistical scenarios for expected differences between Spherox and microfracture [(15), p76, Table 6]

Expected difference: Spherox minus Microfracture	**Standard deviation**	***n*** **per group (80% power)**
–2	10	39
	15	85
0	10	23
	15	50
+2	10	16
	15	34

Sample-size could be reduced by using information from all visits in a repeated-measure ANCOVA to estimate the overall effect. Assuming 4 time points and a correlation between different time points of $r = 0.8$ (strong correlation = conservative assumption), a 10% reduction in sample size would achieve the same power (20) (15).

To prove non-inferiority of Spherox in comparison with microfracture after 24 months, 45 patients (excluding drop-outs) were recommended in each treatment group for an expected Spherox minus microfracture difference of about zero. As the expected drop-out rate in Group A was about 7.5% + 8% =15.5% and in Group B was 7.5%, 52 patients in the Spherox group and 49 patients in the microfracture group were recommended to prove non-inferiority (15).

The given sample size for Step 2 results in a power of >90% for Step 1 if an improvement of at least 16 points of Spherox versus baseline (Day 0) is observed with a standard deviation of 1.41×15 for the difference (15).

Group assignment

"Central telephone randomization" was used to assign patients to either the Spherox or microfracture groups. A randomisation list was prepared and retained by StatConsult GmbH. When a patient suitable for inclusion according to all inclusion/exclusion criteria (including arthroscopically determined defect size) was identified, the investigator contacted StatConsult by telephone hotline and was informed of the treatment the patient was to receive based on the randomisation list (15).

Data sets analysed

The principal efficacy assessment was based on the intention to treat (ITT1) population, with supporting ITT2 and per protocol (PP) analyses.

- *Safety population:* All patients who signed informed consent form and were randomized successfully.
- *ITT1 population:* All successfully randomized patients who received either Spherox on the day of implantation or microfracture on the day of arthroscopy, and completed the KOOS questionnaire at baseline and/or Day 0'.

- *ITT2 population*: A supplementary ITT population representing patients who were successfully randomized and completed the KOOS questionnaire at baseline and/or Day 0 but who for whatever reason, were not treated.
- *PP population:* All patients of the ITT1 population without major protocol violations (15).

Table 14. Composition of study populations [(15), p84, sec 11.1, Table 8]

Treatment group	Spherox	Microfracture	All patients
Safety population	52	50	102
ITT2 population	49	50	99
ITT1 population	48	49	97
PP population	[redacted]	[redacted]	[redacted]

Statistical analyses

Objective

The study was designed to test the non-inferiority and possible superiority of Spherox treatment (versus baseline) as well as its long-term efficacy and safety. Ordered hypotheses testing was used with respect to KOOS. The final analysis, presented here, was conducted after 24 months (15).

Primary analysis

The primary analysis was carried out on the change of overall KOOS from Day 0 (baseline) to final assessment (FA) at 24 months. The primary analysis was performed according to a prospectively defined hierarchical scheme.

The statistical hypotheses were tested hierarchically:

- In the first step, relevant clinical improvement of Spherox versus baseline (Day 0) was tested. If the lower bound of the one-sided 97.5% confidence interval of the change in overall KOOS at 24 months versus baseline (Day 0) was greater than 10 percentage points, then relevant clinical improvement was to be considered to have been shown, and the next step (non-inferiority test of Spherox in comparison with microfracture) was performed.

- In the second step, the difference between the improvements in overall KOOS after Spherox minus the improvement in overall KOOS after microfracture was tested, with a hypothesised value of zero and a non-inferiority margin of –8.5 points. Thus, non-inferiority was to be considered proven if the lower bound of the confidence interval for the difference was greater than –8.5. This was the primary analysis.

The same test was additionally used to assess superiority, with superiority to be considered demonstrated (at the descriptive level) if the lower bound of the confidence interval for the difference was greater than zero (according to CPMP/EWP/482/99 (15, 21).

Secondary efficacy analyses

Change of overall and subscores of the KOOS (pain, other symptoms, function in daily living [activities of daily living, ADL], function in sport and recreation (sport/rec), knee-related quality of life [QoL]) were compared between Spherox and microfracture from baseline (Day 0' for Spherox or Day 0 for microfracture) to 12 months (interim analysis) and 24 months (this analysis). The analysis methods for these variables were similar to the primary analysis, but should be interpreted in an exploratory sense.

The other secondary efficacy variables were investigated at the descriptive level. At each time point, 95% confidence intervals were provided between treatment groups as well as changes within treatment groups between baseline and time point, as applicable (15).

Analysis of subgroups and covariates

The following age subgroups were investigated: 18–34 years inclusive and 35–50 years inclusive. No comparison of sites was undertaken within the scope of the present analysis. Although an analysis by compliance with the post-operative rehabilitation programme was planned, compliance was very good rendering such analyses meaningless (15).

Additional analyses

The primary endpoint was analysed by smoking, BMI, state of origin, and symptom duration. Superiority of Spherox in comparison with microfracture was also tested for MOCART (including each of its subscores), Bern Score, ICRS Visual Histological score, and ICRS II Histological score. Furthermore, additional responder analyses were performed (15).

Protocol deviation

A protocol deviation was defined as any non-compliance (by the patient, the investigator, or the study site staff) with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. Protocol violations were classified as “major” or “minor” at the Data Review Meeting on 23th March 2017. Thirty-six patients with major protocol violations were excluded from the PP population (15).

Handling of missing data

The Last Observation Carried Forward (LOCF) method for the ITT assessment was used to impute single, individual missing scores/questionnaires after at least one “post study therapy” observation. This procedure was not used for drop-out patients randomised to Spherox who withdrew before Day 0’ (15).

B.2.4.2 Phase II trial

A total of 163 patients were screened for eligibility against the inclusion and exclusion criteria detailed above. 75 patients were deemed eligible and were enrolled in the study. Two patients were taken out of the intention-to-treat (ITT) analysis prior to implantation, due to spheroids failing to form in culture. These two patients are however included in the safety analysis set.

Among the 73 patients in the ITT population, major protocol violations led to exclusion of [redacted] patients from the per protocol analysis population, which thus comprised [redacted] patients for this four year follow up analysis. Note that [redacted] of the [redacted] patients withdrew, or were withdrawn, prematurely: [redacted] in the low-dose group, [redacted] in the medium-dose group and [redacted] in the high-dose group. Apart from these, the main reason for violations of the study protocol were out of range doses; predominantly too low doses due to inadequate cell proliferation in culture.

The three analysis population sizes for the four year assessment are summarised in Table 15.

Table 15: Population size at 4 years

Dose group	Low	Medium	High	All
Safety population	[redacted]	[redacted]	[redacted]	75
ITT population	[redacted]	[redacted]	[redacted]	73
PP population	[redacted]	[redacted]	[redacted]	[redacted]

Source: co.don AG CSR (15)

The primary analysis was performed according to a prospectively defined hierarchical scheme: First the primary efficacy variable at final assessment was compared with its baseline value for the high-dose group, next the same comparison was made for the medium-dose group and next the same for the low-dose group. Finally an exploratory between-group comparison was performed.

Secondary analyses were performed, at a descriptive level, in an analogous manner where the structure of the variable allowed this; in other cases, appropriate descriptive statistics were provided.

Safety was analysed by tabulation of adverse events (numbers of reports and numbers/percentages of patients affected) and by presenting descriptive statistics for vital signs, body weight and body mass index, and standard laboratory variables (16).

Power of the trial – sample size calculations

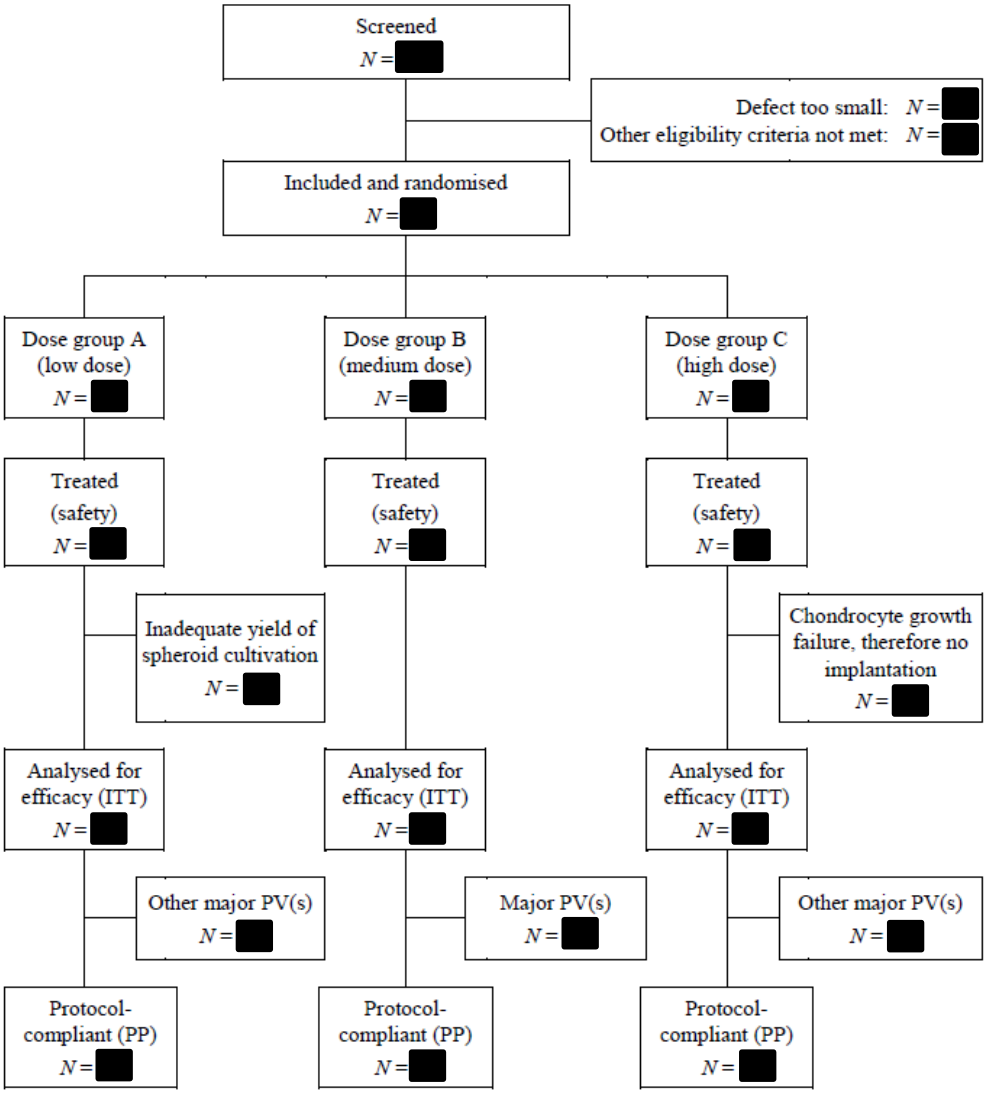
There was no imputation of missing demographic, baseline or safety data. For efficacy data, the statistical analysis plan detailed three different methods in which missing data was imputed. Firstly, imputation by average where for the primary variable, if one or two items were missing, they are imputed by average of remaining items. As an average estimate, the median is used. For all other efficacy variables, the single missing items were imputed by the median of the remaining items for that patient. The rule was not applied for binary ('yes'/'no') variables.

For all the missing values that could not be handled by the first rule, the "last observation carried forward" rule was used. Missing values could be imputed by values measured before, otherwise they were not imputed. A complete case analysis was performed for the primary endpoint, in which analysis without LOCF imputation was carried out for the ITT and PP populations. The differences were to be interpreted on an exploratory basis (16).

Participant flow in the relevant randomised controlled trials

A summary of the patient flow through the clinical trial is provided in Figure 4.

Figure 4: Patient disposition



PV: protocol violation

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Please see below a summary of the quality assessment carried out for the phase III and Phase II above described. A complete quality assessment for each trial can be found in Appendix D.

Study question	Phase III trial	Phase II trial
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Phase III trial

Primary efficacy analysis

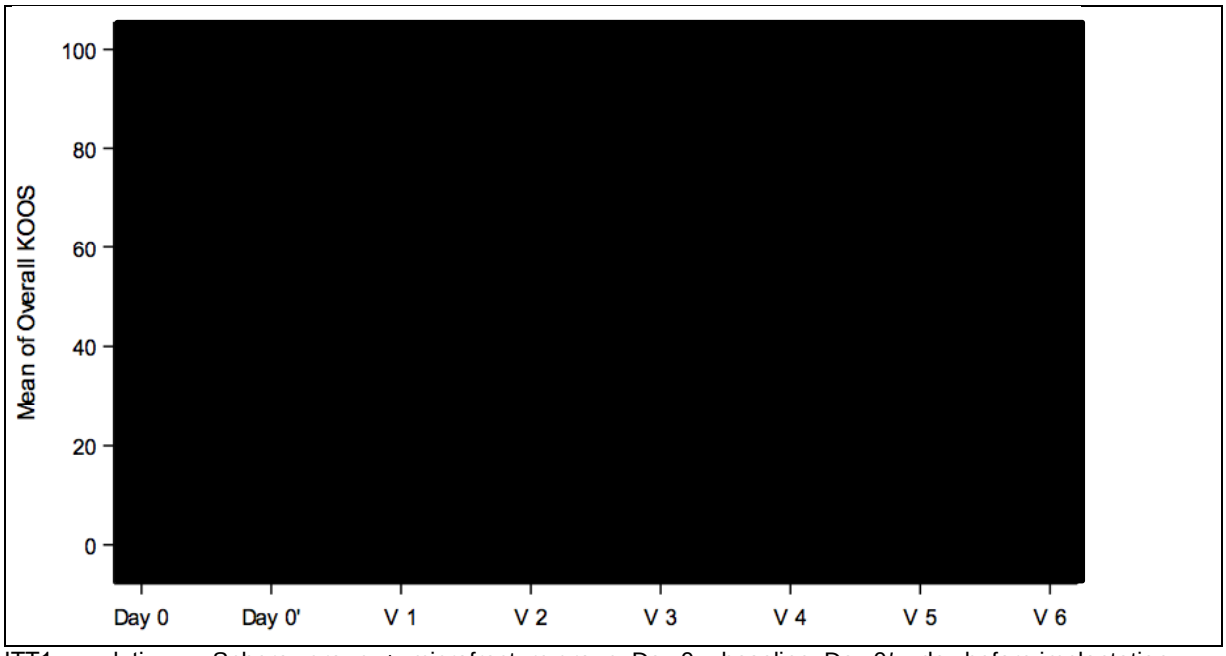
The primary variable was the overall KOOS, calculated by averaging the normalised subscores for the ITT1 population. Descriptive statistics for overall KOOS at each study visit and the change at each visit from baseline (the arithmetic difference) are summarised in Table 16. Increases are observed in both treatment groups over the 24-month period. The increases are apparent after 12 months. The plot of absolute

values for overall KOOS illustrates the general trend (Figure 5). The comparable differences between baseline and Visit 6 indicates the similarity in response for the two treatment groups (Figure 6). The Spherox group showed greater changes at all visits from three months onward than microfracture group. In both groups, an initial decrease, with a minimum at Visit 1, may be associated with operation-related complaints.

Table 16. Overall KOOS at each visit (ITT1 population) [(15), p89, sec 11.4.1.1, Table 13]

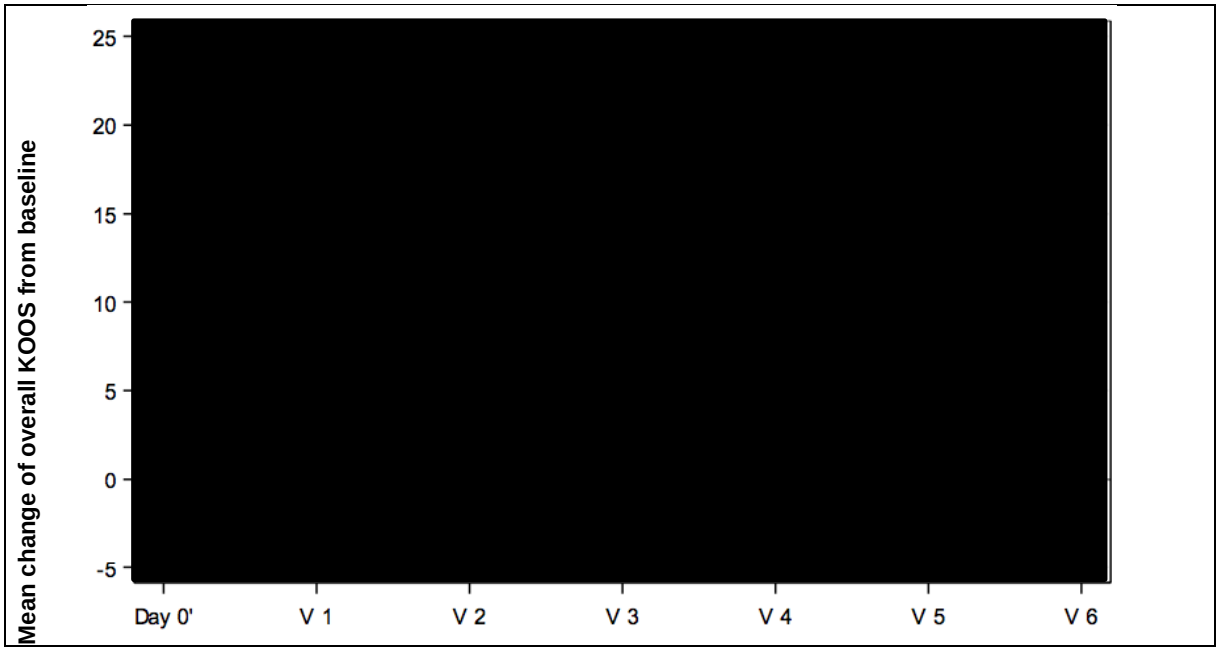
Treatment group **Visit**		**Spherox** *N* = 48	**Microfracture** *N* = 49
Values at each visit			
Pre-arthroscopy (baseline)	mean ± SD	56.6 ± 15.4	51.7 ± 16.5
median		53	51
Pre-implantation (Day 0')	mean ± SD	61.1 ± 18.2	–
median		58	
Visit 1 (6 weeks)	mean ± SD	52.1 ± 17.4	47.0 ± 16.1
median		56	48
Visit 2 (3 months)	mean ± SD	68.4 ± 17.6	57.9 ± 16.9
median		71	56
Visit 3 (6 months)	mean ± SD	74.2 ± 18.0	67.2 ± 16.7
median		77	69
Visit 4 (12 months)	mean ± SD	78.7 ± 18.6	68.1 ± 18.6
median		84	70
Visit 5 (18 months)	mean ± SD	[redacted]	[redacted]
median			
Visit 6 (24 months)	mean ± SD	[redacted]	[redacted]
median			
Changes from baseline			
Pre-implantation (Day 0')	mean ± SD	4.5 ± 13.3	–
median		1	
Visit 1 (6 weeks)	mean ± SD	–4.5 ± 18.2	–4.7 ± 16.0
median		–4	–4
Visit 2 (3 months)	mean ± SD	11.9 ± 19.9	6.2 ± 17.8
median		9	6
Visit 3 (6 months)	mean ± SD	17.7 ± 18.3	15.5 ± 14.7
median		14	15
Visit 4 (12 months)	mean ± SD	22.2 ± 18.3	16.4 ± 15.1
median		20	15
Visit 5 (18 months)	mean ± SD	[redacted]	[redacted]
median			
Visit 6 (24 months)	mean ± SD	[redacted]	[redacted]
median			

Figure 5: Overall KOOS at each visit – mean values [(15), p90, sec 11.4.1.1, Figure 3]



ITT1 population. ○, Spherox group; +, microfracture group. Day 0 = baseline. Day 0′ = day before implantation. y-axis maximum range 0–100. Visits V1–V6 took place 6 weeks and 3, 6, 12, 18, and 24 months after implantation.

Figure 6: Overall KOOS at each visit – changes from baseline (Day 0)



ITT1 population. ○, Spherox group; +, microfracture group. Day 0 = baseline. Day 0′ = day before implantation. y-axis maximum range 0–100. Visits V1–V6 took place 6 weeks and 3, 6, 12, 18 and 24 months after implantation.

The hierarchical statistical testing yielded the following results (15): *Step 1: Test for relevant clinical improvement from baseline to Visit 6 for the Spherox group:*

Difference = [redacted], $p < 0.0001$

[For comparison, though not part of Step 1: Difference for microfracture = [redacted], $p < 0.0001$.]

- Step 2: *Repeated-measures ANCOVA testing for non-inferiority of Spherox vis-à-vis microfracture (least-square mean difference from baseline for Spherox minus mean difference from baseline for microfracture):*

Difference = [redacted] ($p < 0.0001$) with lower bound of CI equal to [redacted].

Since this lower bound has a value greater than –8.5, non-inferiority is formally demonstrated. Thus the prospectively formulated, confirmatory aim of the study was achieved. All remaining statistical tests were performed at the descriptive level.

The test for superiority of Spherox vis-à-vis microfracture involved the difference (i.e., mean difference from baseline for Spherox minus mean difference from baseline for microfracture) already calculated. [redacted]. It should however be noted that the study was powered for non-inferiority, not for superiority.

Analysis of variance (ANOVA) yielded the following least-squares means with corresponding standard errors and 95% confidence intervals:

Spherox: [redacted]

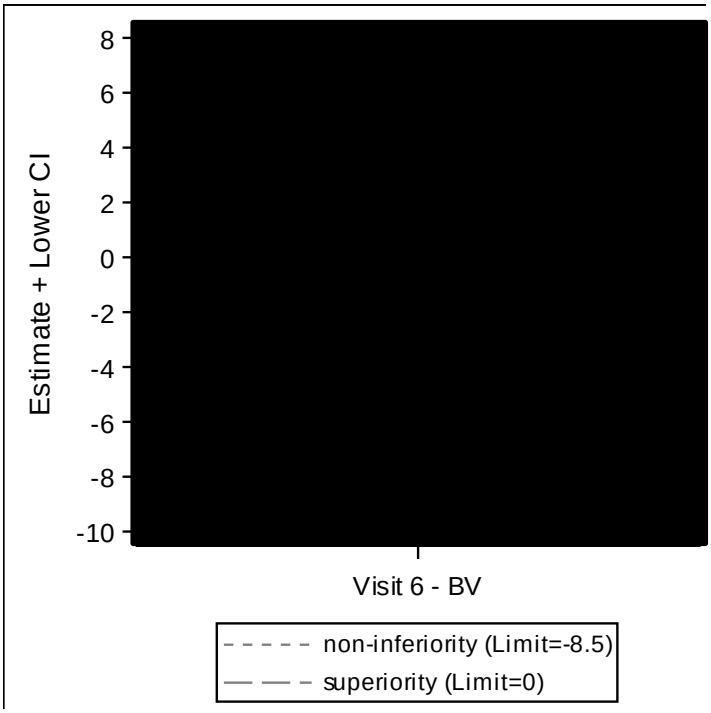
Microfracture: [redacted]

The Satterthwaite test was also performed, again at the descriptive level, to investigate non-inferiority of Spherox vis-à-vis microfracture gave the following result:

Difference = [redacted] with lower bound of CI equal to [redacted].

By the same criterion as above, since this lower bound has a value greater than –8.5 but smaller than zero, the result of this test demonstrates non-inferiority [redacted]. Thus, the result of the Satterthwaite test supports that of the primary analysis by ANCOVA (15).

Figure 7: Overall KOOS, change from baseline to Visit 6: Difference between Spherox and microfracture



Secondary efficacy outcomes

KOOS subscores

The KOOS subscores yielded the same qualitative result as the full-KOOS analysis, i.e., for each of these non-inferiority was demonstrated. Superiority was shown in the KOOS subscore “function in daily living” with statistical significance by using the additional post hoc repeated-measures ANCOVA analysis.

KOOS subscore values for the ITT1 population are shown for selected visits in Table 17 (‘overall’ values are repeated here for ease of comparison) and results are

summarised in Table 18 by displaying the changes from baseline or Day 0' to Visit 6 (24 months after treatment).

There was a substantial improvement across all measures (greater in the Spherox group than in the microfracture group) ranging from approximately [redacted] in the Spherox group ([redacted] in the microfracture group). Significance testing was repeated for each of the KOOS-related secondary variables (Table 19).

The significance testing performed for the primary analysis was repeated for each of the KOOS-related secondary variables by repeated-measures ANCOVA, as used for the primary analysis and by the t test.

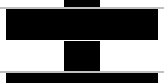
The ANCOVA analysis for the subscores gave a scatter of values, in particular of the lower bound of the CI, which ranged from [redacted] (for ‘function in daily living’, implying superiority at the descriptive level) to [redacted]. Apart from ‘function in daily living’, all other KOOS subcores in ANCOVA tests, and all KOOS subcores in *t* tests, gave the same qualitative result as the full-KOOS analysis had done: non-inferiority (lower confidence limit > –8.5) was demonstrated at the descriptive level, [redacted].(15).

Table 17: Analysis of KOOS and its subscores: values at baseline (Day 0), Day 0′, and Visits 2, 4, 5 and 6 (ITT1 population)

	Treatment group: Variable	Spherox *N* = 48		Microfracture *N* = 49	
Value at baseline	Overall KOOS	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	[redacted]
Value on Day 0′	Overall KOOS	[redacted]	[redacted]	[redacted]	
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	
Value at Visit 2	Overall KOOS	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	[redacted]
Value at Visit 4	Overall KOOS	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	[redacted]
Value at Visit 5	Overall KOOS	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	[redacted]
Value at Visit 6	Overall KOOS	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘pain’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘other symptoms’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in daily living’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘function in sport and recreation’	[redacted]	[redacted]	[redacted]	[redacted]
	KOOS ‘knee-related quality of life’	[redacted]	[redacted]	[redacted]	[redacted]

Source co.don AG CSR (15); Mean values ± SD (left) and medians (right) are shown throughout.

Table 18. Analysis of secondary KOOS subscores: changes from baseline (Day 0) and from Day 0' to Visit 6 (ITT1 population) [(15), p97, Table 15]

	Variable	Spherox *N* = 48	Microfracture *N* = 49
Change from baseline	Overall KOOS*		
	KOOS "symptoms"		
	KOOS "pain"		
	KOOS "function in daily living"		
	KOOS "function in sport and recreation"		
	KOOS "knee-related quality of life"		
Change from Day 0'	Overall KOOS*		

Mean values ± SD (above) and medians (below) are shown. *Primary variable, shown here for comparison)

Table 19. KOOS subscores analysed by repeated-measures ANCOVA: changes from baseline (Day 0) and from Day 0′ to Visit 6 (ITT1 population)) [(15), p98, Table 17]

	Treatment group: Variable	Difference *N* = 48	Lower CL *N* = 49
Change from baseline	Overall KOOS		
	KOOS "symptoms"		
	KOOS "pain"		
	KOOS "function in daily living"		
	KOOS "function in sport and recreation"		
	KOOS "knee-related quality of life"		

*Primary variable, shown here for comparison; the difference for 'Spherox minus microfracture' is shown.

MOCART score

Company evidence submission template for Autologous chondrocyte implantation with Spherox for treating articular cartilage defects [ID851]

MOCART scores in all treatment groups showed a similar trend: an increase from the assumed low baseline value to Visit 2, and a further increase to Visits 4, 5, and 6 (Table 20.;Figure 8). Between Visit 2 and Visit 4, there was a general improvement in median MOCART score (from around 60–70 to around 80). The Spherox group showed slightly higher values than the microfracture group at both visits. At Visits 5 and 6 were similar in the two treatment groups. The mean value for the Spherox group was lower than for the microfracture group at Visit 6 (median, quartile and maximum values were the similar) (Table 20.). The implication is that the presence of low-value outliers in the Spherox group impacted the difference in means; this is confirmed in the box plot (Figure 8).

The following differences (score in the Spherox group minus score in the microfracture group) were observed at the 12-month and 24-month visits:

Visit 4: [redacted]

Visit 6: [redacted]

[redacted]; the non-inferiority test result was at the pre-specified limit (–8.500) (15).

Among the individual MOCART items, response to treatment, and the difference between treatment groups, varied. The items showing the greatest improvements were: 1 (defect repair), 3 (surface), 5 (signal intensity), 7 (subchondral bone), and 9 (synovitis). In both treatment groups, all items showed an increase compared with the assumed low values at baseline. A systematic difference between the two treatment groups could not be established (15).

Table 20. MOCART scores at Visits 2, 4, 5 and 6 (ITT1 population) [(15), p105, Table 18]

	Visit 2 (3 months)		Visit 4 (12 months)	
	Treatment group		Treatment group	
Mean ± SD				
Minimum				
Lower quartile				
Median				
Upper quartile				
Maximum				
	Visit 5 (18 months)		Visit 6 (24 months)	
Mean ± SD				
Minimum				
Lower quartile				
Median				
Upper quartile				
Maximum				

Differences from total population sizes are due to missing results.

Figure 8: Box plots for MOCART score at Visits 2, 4, 5 and 6 (3, 12, 18 and 24 months) [(15), p105, Figure 17]

ITT1 population.

Arthroscopic assessment of cartilage repair

This was only assessed for those patients who had consented to the additional arthroscopy). On account of a single patient in the Spherox group with a missing baseline value, the safety population is considered here. Assessment of repair according to ICRS at Visit 6 for patients who had consented to the additional arthroscopy ( ) is summarised in Table 21.

[redacted] (Satterthwaite analysis of the difference between the two treatment groups yielded a lower limit for the confidence interval of [redacted]) (15).

Table 21. Cartilage repair assessment at Visit 6 (ITT1 population) [(15), , p112, Table 30]

Assessment	Spherox	Microfracture
Grade I (normal)	[redacted]	[redacted]
Grade II (nearly normal)	[redacted]	[redacted]
Grade III (abnormal)	[redacted]	[redacted]
Grade IV (severely abnormal)	[redacted]	[redacted]
All	[redacted]	[redacted]

Numbers of patients are given.

ICRS visual histological assessment

Results of the ICRS visual histological assessment are summarised in Table 22. In summary, a normal presence of predominantly viable cells ([redacted] patients, respectively) and a normal cartilage mineralization (all patients) was observed in the repair tissue of the majority of R-biopsies. Subchondral bone was also predominantly normal ([redacted] patients). Greater variability was observed in other histological features of the repair tissue. Fewer than [redacted] of patients, in both treatment groups, had a smooth cartilage surface.

These results indicated that both the cell transplant and the microfracture resulted in the generation of a cartilage repair tissue of 'good' to 'mixed' as evaluated by visual histological assessment. Results tended to be slightly better in the ACT3D-CS group than in the microfracture group (with the exception of 'surface'), but the small numbers of patients investigated in each group renders this observation uncertain (15).

Table 22: Cartilage repair assessment at Visit 6 (ITT1 population) [(15), p113, Table 31]

Criterion	Result	No. of patients	
		Spherox N=10	Microfracture N=7
Surface	Smooth/continuous	[redacted]	[redacted]
	Discontinuities/irregularities	[redacted]	[redacted]
Matrix	Hyaline	[redacted]	[redacted]
	Mixture: hyaline/fibrocartilage	[redacted]	[redacted]
	Fibrocartilage	[redacted]	[redacted]
	Fibrous tissue	[redacted]	[redacted]
Cell distribution	Columnar	[redacted]	[redacted]
	Mixed/columnar clusters	[redacted]	[redacted]

	Clusters	[redacted]	[redacted]
	Individual cells / disorganised	[redacted]	[redacted]
Cell population viability	Predominantly viable	[redacted]	[redacted]
	Partially viable	[redacted]	[redacted]
	<10% viable		[redacted]
Subchondral bone	Normal	[redacted]	[redacted]
	Increased remodelling	[redacted]	[redacted]
	Bone necrosis / granulation tissue	[redacted]	[redacted]
	Detached/fracture/callus at base	[redacted]	[redacted]
Cartilage mineralisation	Normal	[redacted]	[redacted]
	Abnormal/inappropriate location	[redacted]	[redacted]

Numbers of patients are given; patients "missing" are omitted.

Bern score

Seventeen patients consented to the R-biopsy with the arthroscopy. Scores were almost identical for the two treatment groups (Table 23) (15).

Table 23. Bern score at Visit 6 (ITT1 population) [(15), p117, Table 34]

	Spherox *N* = 10	**Microfracture** *N* = 7
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

Numbers of patients are given.

Other histological assessment scores

Assessment was performed according to the ICRS II histological scoring values were slightly better in the Spherox group (Table 24). The mean and median values were notably better in the Spherox group. The difference between the two treatment groups yielded a lower limit for the confidence interval of [redacted] (Satterthwaite analysis), so [redacted]. Non-inferiority of the ACT3D-CS treatment was supported by this test, in spite of the extreme underpowering by the small numbers in the treatment groups for this test – only [redacted] and [redacted] patients respectively). (15).

Table 24. ICRS II histological score (ITT1 population) [(15), p121, Table 35]

		Spherox	Microfracture
Overall	Mean ± SD	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Range	[redacted]	[redacted]
Surface/superficial assessment	Mean ± SD	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Range	[redacted]	[redacted]
Mid/deep zone assessment	Mean ± SD	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Range	[redacted]	[redacted]

Numbers of patients are given.

IKDC Score

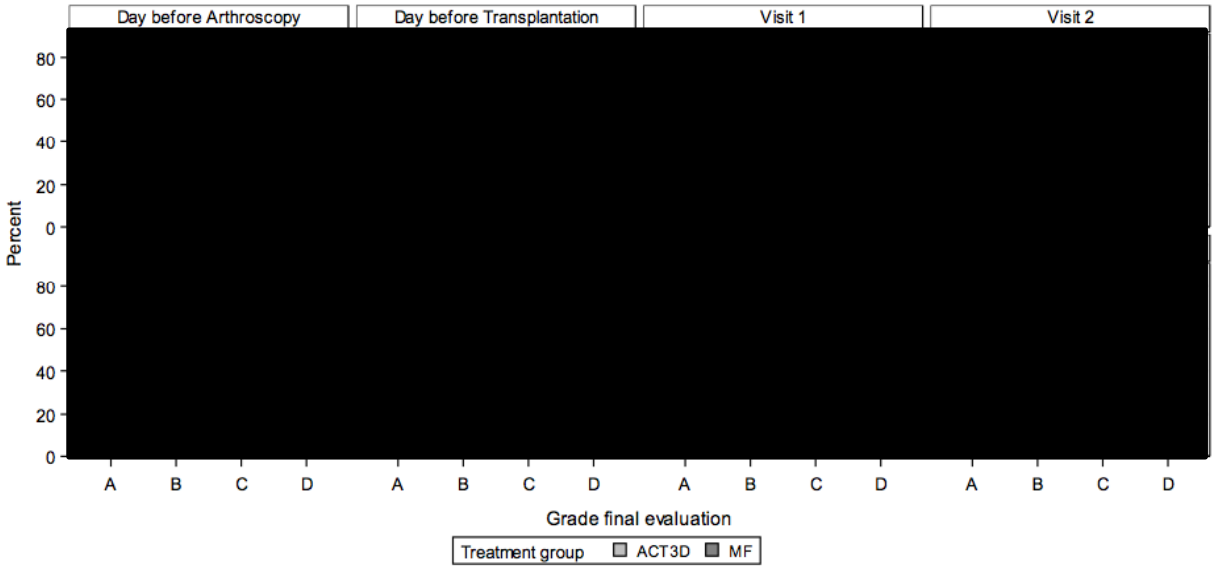
The overall IKDC score was assessed using grades A–D on the "2000 IKDC Knee Examination Form". In both groups, worse ratings were observed at Visit 1 compared with the pre-implantation visit(s). An increase in numbers of patients with the rating "A" at Visits 4–6 was seen in both treatment groups and is indicative of general improvement between these visits. The overall improvement was greater in the Spherox group. (Table 25). The time courses of the overall grading according to IKDC, for the total patient cohort, are shown in Figure 9 (15).

Table 25. IKDC Knee Examination Form – overall assessment (ITT1 population) [(15), p122, Table 36]

Treatment group:	**Spherox group**				**Microfracture group**			
IKDC Grade:	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Pre-arthroscopy day	26	12	9	–	25	18	4	2
Pre-implantation day	26	18	4	–	n.a.			
Visit 1 (6 weeks)	14	12	7	15	13	16	10	10
Visit 2 (3 months)	26	14	4	4	21	22	5	1
Visit 3 (6 months)	34	10	3	1	31	15	3	–
Visit 4 (12 months)	41	6	1	–	34	14	1	–
Visit 5 (18 months)	[redacted]							
Visit 6 (24 months)	[redacted]							

Numbers of patients with the respective grade at each visit are shown. Source: Table 14.2.3.13.1.

Figure 9: Bar chart for IKDC Knee Examination Form (1)



ITT1 population.

IKDC Current Health Assessment Form – subscores

The IKDC Current Health Assessment Form subscore analysis was similar to that for the primary and secondary variables associated with KOOS. Table 26 shows the ANOVA results for all the IKDC Current Health Assessment Form subscores, and Table 27 shows the corresponding results obtained for Visit 4. Physical functioning at Visit 4 was the only subscore to demonstrate (descriptive) significance (Table 26) (15).

Table 26. IKDC Current Health Assessment subscores: changes from baseline (Day 0) to Visit 4 (ITT1 population) [(15), p119, Table 35]

	Treatment group: IKDC subscore	**Spherox**	**Microfracture**	p-value
Change from baseline to Visit 4	Physical functioning			
	Role physical			
	Bodily pain			
	General health			
	Vitality			
	Social functioning			
	Role emotional			

	Mental health	[redacted]	[redacted]	[redacted]
	Physical component summary	[redacted]	[redacted]	[redacted]
	Mental component summary	[redacted]	[redacted]	[redacted]

Subscores are shown on the scale 0–100 (see text). Mean values ± SD are shown. *p* values are taken from ANOVA.

Table 27: IKDC Current Health Assessment subscores: changes from baseline (Day 0) to Visit 6 (ITT1 population)

	Treatment group: IKDC subscore	**Spherox**	**Microfracture**	*p-value*
Change from baseline to Visit 6	Physical functioning	[redacted]	[redacted]	[redacted]
	Role physical	[redacted]	[redacted]	[redacted]
	Bodily pain	[redacted]	[redacted]	[redacted]
	General health	[redacted]	[redacted]	[redacted]
	Vitality	[redacted]	[redacted]	[redacted]
	Social functioning	[redacted]	[redacted]	[redacted]
	Role emotional	[redacted]	[redacted]	[redacted]
	Mental health	[redacted]	[redacted]	[redacted]
	Physical component summary	[redacted]	[redacted]	[redacted]
	Mental component summary	[redacted]	[redacted]	[redacted]

Subscores are shown on the scale 0–100 (see text). Mean values ± SD are shown. *p* values are taken from ANOVA.

IKDC Subjective Knee Evaluation Form

Slightly higher baseline values from IKDC Subjective Knee Evaluation Form were recorded in the Spherox group than in the microfracture group. Day 0' values for the Spherox group, were similar to baseline (Table 28), suggesting the absence of

spontaneous healing. In both treatment groups, values were lower at Visit 1, but the patients' assessment improved thereafter (15).

Table 28. IKDC Subjective Knee Evaluation Form (ITT1 population) [(15), 127, Table 40]

Treatment group Visit	Spherox group *N* = 48	Microfracture group *N* = 49
Values at each visit		
Pre-arthroscopy (baseline)	54.5 ± 15.9	47.8 ± 14.6
Pre-implantation (Day 0')	56.3 ± 16.6	n.a.
Visit 1 (6 weeks)	46.4 ± 15.2	40.0 ± 14.4
Visit 2 (3 months)	63.0 ± 17.1	52.6 ± 15.4
Visit 3 (6 months)	69.3 ± 17.6	60.5 ± 15.4
Visit 4 (12 months)	75.2 ± 18.5	64.6 ± 19.9
Visit 5 (18 months)	[redacted]	[redacted]
Visit 6 24 months)	[redacted]	[redacted]
Changes from baseline		
Pre-implantation (Day 0')	1.9 ± 10.8	n.a.
Visit 1 (6 weeks)	–8.0 ± 19.3	–7.8 ± 14.5
Visit 2 (3 months)	8.6 ± 19.4	4.8 ± 13.9
Visit 3 (6 months)	14.9 ± 17.8	12.7 ± 14.0
Visit 4 (12 months)	20.8 ± 18.7	16.8 ± 15.6
Visit 5 (18 months)	[redacted]	[redacted]
Visit 6 24 months)	[redacted]	[redacted]

Mean values ± SD are shown throughout. Baseline = Day 0.

Modified Lysholm score

Baseline modified Lysholm scores were similar between the treatment groups at (Day 0). At all study visits (except Visit 5) the mean improvement was greater in the Spherox group than in the microfracture group, however, this was not statistically significant (p = [redacted] for Visit 4 and [redacted] for Visit 6) (Table 29) (15).

Table 29. Modified Lysholm score (ITT1 population) [(15), p128, Table 41]

Treatment group: Visit	**Spherox** *N* = 48	**Microfracture** *N* = 49
Values at each visit		
Pre-arthroscopy (baseline)	16.8 ± 4.0	16.0 ± 3.3
Pre-implantation (Day 0')	18.5 ± 3.7	n.a.
Visit 1 (6 weeks)	15.4 ± 2.7	14.2 ± 3.7
Visit 2 (3 months)	19.1 ± 3.4	17.7 ± 3.8
Visit 3 (6 months)	20.4 ± 3.0	19.4 ± 3.4
Visit 4 (12 months)	21.1 ± 3.0	19.8 ± 3.2
Visit 5 (18 months)	[redacted]	[redacted]
Visit 6 (24 months)	[redacted]	[redacted]
Changes from baseline		

Pre-implantation (Day 0')	1.7 ± 3.3	n.a.
Visit 1 (6 weeks)	–1.4 ± 3.9	–1.8 ± 3.3
Visit 2 (3 months)	2.3 ± 4.7	1.7 ± 3.6
Visit 3 (6 months)	3.6 ± 4.0	3.4 ± 3.2
Visit 4 (12 months)	4.3 ± 4.3	3.8 ± 3.0
Visit 5 (18 months)	[redacted]	[redacted]
Visit 6 (24 months)	[redacted]	[redacted]

Mean values ± SD are shown throughout. Source: Tables 14.2.3.16.1.

Responder analyses

Responder analyses in ITT1 at the 12 and 24-month assessments using KOOS score increases of at least 8 and 10 points from baseline showed a greater percentage of responders in the Spherox group than in the microfracture group (Table 30) (15).

Table 30. Responder analysis: Overall KOOS [(15), p137, Table 47]

Visit	Criterion	Spherox *n* / *N* (%)	Microfracture *n* / *N* (%)	Difference (percentage points)
12 months	8-point	[redacted]	[redacted]	[redacted]
	10-point	[redacted]	[redacted]	[redacted]
24 months	8-point	[redacted]	[redacted]	[redacted]
	10-point	[redacted]	[redacted]	[redacted]

ITT1 population. Numbers *n*/*N* and percentages (%) of responders after 12 months are shown, with the calculated percentage-point difference in the right-hand column; a positive difference is in favour of Spherox.

Additional (post hoc) efficacy analyses

The following additional analysis was conducted to demonstrate superiority of Spherox compared with MF for the treatment of cartilage defects of knee joints.

This original study was designed in 2008 and was based on the reference study published by Saris et al 2008 (19) with ChondroCelect, where a 2.5 % points one-sided test was used. Furthermore, their modified primary endpoint was the test of non-inferiority of KOOS (change from baseline) (next to the other primary endpoint of superiority for structural repair/histology). Therefore the design of the recent study was based on most current knowledge at that time.

The original analyses of overall KOOS and subscores were realized for non-inferiority of MF compared to Spherox using a one-sided confidence level of alpha=0.025 as preferred in ICH-E9 (section V.E). Nevertheless, in analyzing changes to baseline in overall KOOS, [redacted] using this strict confidence level of alpha=0.025 (one-sided). Thus, when the results of the trial became available, they suggested an alternative

interpretation so that we repeated analyses using a one-sided confidence level of alpha=0.05 to show superiority of Spherox over MF for:

- Overall KOOS as well as for the subscores ADL, Quality of Life (QoL) and other symptoms for ITT population
- Secondarily, for IKDC Assessment Form for ITT population
- Overall KOOS as well as for the subscores pain, ADL, QoL and other symptoms for PP population
- Secondarily, for IKDC Assessment Form for PP population

Statistical method: Increasing the significance level for the one-sided confidence limit (CL) from α = 0.025 (97.5% -CL) to α = 0.05 (95.0% -CL), since analysis were carried out independently of SAP (without consideration of the hierarchical approach) (15).

Overall KOOS und Subscores: Non-Inferiority / Superiority via repeated measure analysis of covariance (ANCOVA)

Secondary endpoints: Non-Inferiority / Superiority via T-Test

Additional analysis results

In the primary analysis, in the assessment of 'overall KOOS' for the ITT population, both the treatment under investigation and the reference treatment yielded a statistically significant improvement, relative to baseline. Superiority was demonstrated with a lower confidence limit of [redacted] (above zero).

The KOOS subscores yielded almost the same qualitative result as the full-KOOS analysis, i.e., for each of them non-inferiority was demonstrated, and superiority was shown for the subscores symptoms, function in daily living and knee-related quality of life. These results were confirmed in the PP population. In addition, in this population, superiority was also shown for the subscore pain.

Superiority was also shown when analysing the change of IKDC current health assessment form – physical functioning in the ITT population as well as in the PP population.

In summary, statistical significance testing, both at the level of the primary analysis and at the level of the secondary KOOS related variables, supported the non-inferiority and established superiority of the Spherox treatment compared with microfracture.

There were no fatal adverse events in this trial. There were four serious adverse events for patients in the Spherox group (abdominal neoplasm, cystitis, Hodgkin's disease, malaise; all treatment-unrelated) and six for patients in the microfracture group (deep vein thrombosis, probably treatment-related; joint adhesion and arthralgia, both possibly treatment-related; meniscus lesion, unlikely to be treatment-related; cellulitis and cartilage injury, treatment-unrelated).

In summary, efficacy analyses showed a clear improvement in the patients' condition in both treatment groups. The statistical testing demonstrated non-inferiority of Spherox compared with microfracture, and superiority was demonstrated for overall KOOS as well as for the subscores symptoms, function in daily living and knee-related quality of life (15).

B.2.6.2 Phase II trial

The primary variable was the overall KOOS, was calculated for the intention-to-treat population (N = 73) by averaging the normalised subscores. The primary analysis was that of the overall KOOS 12 months after implantation. The total KOOS score of each subscale has to be summed up and divided by the possible maximum score for the scale. Traditionally in orthopaedics, 100 indicates no problems and 0 indicates extreme problems. The overall KOOS at each study visit (including the 12-month primary analysis) and the change at each visit from baseline (the arithmetic difference) is summarised in Table 31. The results indicate a clear increase for all dose-groups over the first 12-month period in each dose group, with values passing through a minimum at Visit 1. No obvious dose–response relationship in the sense of an increased response to higher doses was observed.

Following the 12-month visit, the improvement in the overall KOOS continued in the low-dose group and medium-dose group, while it decreased slightly in the high-dose group. Between the 24-month and the 36-month visits, a small improvement was seen in each dose group (approximately 2–5 percentage points), and this was maintained at the 48-month visit (16).

Table 31: Overall KOOS at each visit (ITT population)

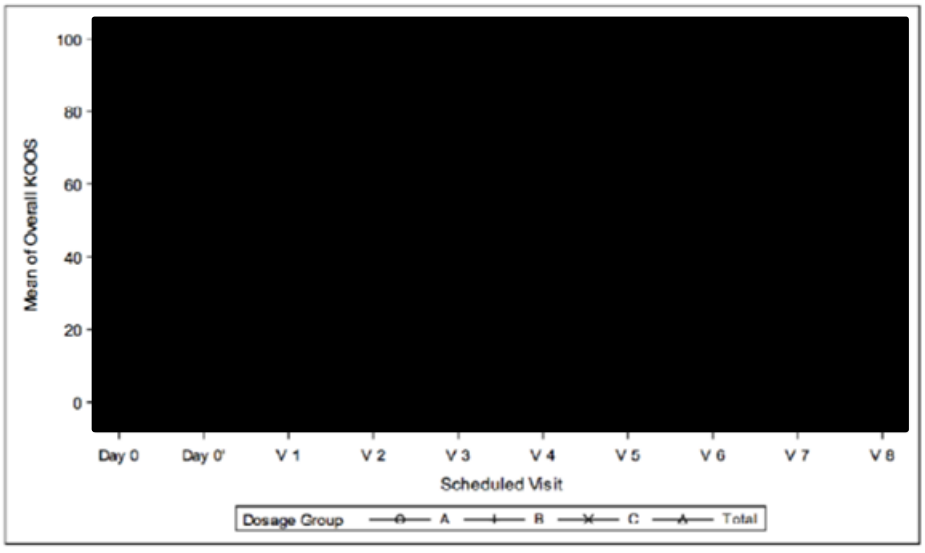
Visit / Dose group:		Low $N = 24$*	Medium $N = 25$	High $N = 24$	All $N = 73$*
Values at each visit					
Pre-arthroscopy (baseline)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4 (12 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 (18 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (24 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7 (36 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8 (48 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline					
Visit 4 (12 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5 (18 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (24 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7 (36 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8 (48 months)	mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]

Baseline = Day 0. [* The baseline value for the overall KOOS of one patient in the low-dose group was missing, because of incomplete response to the ePRO questions. Therefore, $N = 23$ for this group (and $n = 72$ total) at baseline and in the entire lower block.] Source: Table 14.2.1.1.

The results shown in Table 31 are plotted in Figure 10 and Figure 11. These plots also include the corresponding results for the intermediate visits not tabulated above. The general trend is clearly illustrated by the plot of absolute values for overall KOOS (Figure 10), and the similarity in response between the three dose groups is made clear by the very similar course of the differences between baseline and Visit 4 (12

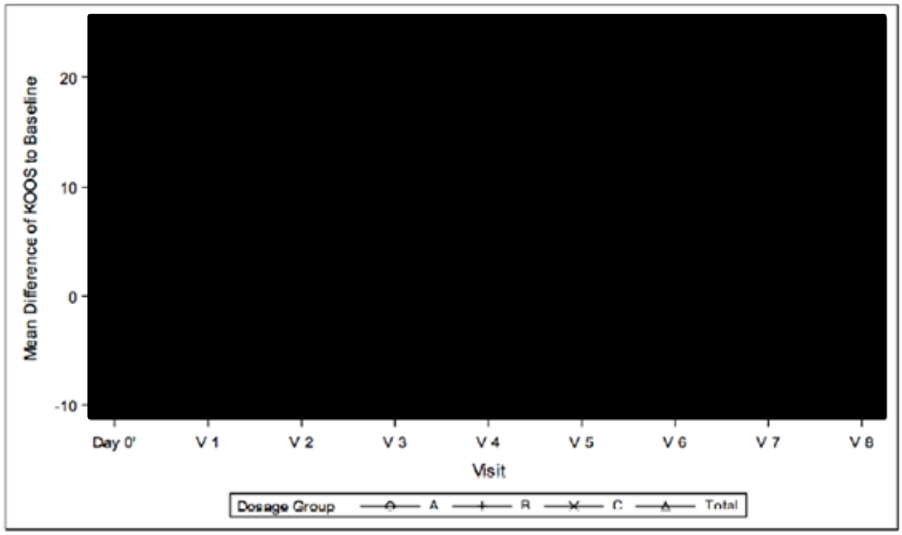
months after implantation), shown in Figure 10. The curve for the high-dose group lies below the others throughout, but the changes with respect to baseline between the groups were similar. An initial decrease, with a minimum at Visit 1 (6 weeks after treatment), is seen for all groups; this is interpreted as being associated with the operation and the patients' limited mobility during the first weeks of the post-surgery period. 12 months after treatment all groups showed roughly constant values. The mean overall KOOS for the total ITT population decreased slightly from Visit 5 to Visit 6 (18 and 24 months); nevertheless, it was still slightly higher (change from baseline [redacted]) at Visit 6 that it had been at Visit 4 (change from baseline [redacted]). A general small increase between 24 and 36 months and maintained at Visit 8 (48 months), as already noted (Figure 11), is also seen. Such changes as there were maybe marginal in view of the scatter of values (compare the respective standard deviations) and may not be clinically relevant. However, it is noteworthy that they were reflected in each of the treatment groups.

Figure 10: Overall KOOS at each visit – mean values



ITT population. Day 0 = baseline. y-axis maximum range 0–100. Visits V1–V8 took place 6 weeks and 3, 6, 12, 18, 24, 36 and 48 months after implantation. A/B/C, low/medium/high dose. Source: Figure 14.2.1.1.

Figure 11: Overall KOOS at each visit - changes from baseline (Day 0)



ITT population. y-axis maximum range 0–100. A/B/C, low/medium/high dose. Source: Figure 14.2.1.2.

The statistical analysis results for the change between the baseline and visit 4 (12 months after implantation) KOOS scores are displayed in Table 32.

Table 32: Change from baseline results

		Difference	p-value	95% C.I.
Change between baseline and visit 4 (12 months)	Low	[redacted]	[redacted]	[redacted]
	Medium	[redacted]	[redacted]	[redacted]
	High	[redacted]	[redacted]	[redacted]
Between-group comparisons	High vs. medium	[redacted]	[redacted]	[redacted]
	Medium vs. low	[redacted]	[redacted]	[redacted]
	High vs. low	[redacted]	[redacted]	[redacted]

From Table 32, we observe that each dose-level was able to yield a statistically significant improvement with respect to baseline values, with the difference between dose groups not found to be statistically significant. The mean between-group differences and their 95% confidence intervals were also calculated, which also led to the same conclusion that no between-group effects were observed (16).

B.2.7 Subgroup analysis

A description of the subgroup analyses conducted can be found below. See Appendix E for results of subgroup analyses.

B.2.7.1 Phase III trial

The results of the KOOS scores in the clinical trial detailed above, were subjected to additional subgroup analyses. In these analyses, the total KOOS score was analysed separately for each of the following categories:

- Age: Patients were stratified prospectively by age into two groups; “18–34 years” comprised 19 ITT1 patients in the Spherox group and 18 patients in the microfracture group, while the age category “35–50 years” comprised 33 patients treated with Spherox and 32 patients treated by microfracture
- Duration of knee symptoms: Pre-screening duration of knee symptoms was recorded for the Spherox -treated patients only
- Patient’s BMI
- Patient’s sex: Male or female

Both age groups showed an increase in overall KOOS from baseline to Visit 6 (24 months). For the younger patients, KOOS overall values at Visit 6 were [redacted] for Spherox and [redacted] for microfracture (for comparison with the baseline value, $p < 0.0001$ in both cases). For the older group an overall KOOS of [redacted] for Spherox and [redacted] for microfracture was found (both p values <0.0001).

No correlation was found between KOOS score at Visit 6 (24 months after treatment) and the previous duration of knee symptoms (p = [redacted] for N = 39 ITT patients). No correlation was found between KOOS score at Visit 6 (24 months after treatment) and BMI (Spearman's p = [redacted] for N = 97 ITT1 patients). No clear sex-related selectivity in quality of response to the one or other treatment could be discerned (15).

Additional analyses were also conducted on a post hoc basis and listed below:

- Age category and smoker status combined
- Responder analysis: A *post hoc* responder analysis was performed with regard to (i) actual numbers of responders, and (ii) the pre-treatment knee-defect severity of the responders and non-responders using the 8-point and 10-point criteria

- Investigation of KOOS score by pain medication

B.2.7.2 Phase II trial

The results of the KOOS scores in the clinical trial detailed above, were subjected to additional subgroup analyses. In these analyses, the total KOOS score was analysed separately for each of the following categories:

- Diagnosis: traumatic cartilage lesion, osteochondritis dissecans, osteoarthritis (but without radiological signs of osteoarthritis, as these constituted exclusion criteria from enrolment), AVN and other diagnoses
- Defect location: femur, tibia or patella
- Patient's age category: 18-34 years or 35-50 years
- Patient's sex: Male or female

In each case statistical tests of change with respect to baseline (within-dose-group and between-dose group comparisons), analogous to the primary efficacy analysis, were performed. No systematic trends that might have reflected underlying differences between the results of treatment at the four visits (12, 24, 36 and 48 months after implantation) were found (16).

B.2.8 Meta-analysis

A retrospective pooled analysis of two trials with Spherox (clinical Phase II and III) was carried out. Both trials are currently being conducted to prove efficacy and safety of Spherox in treating cartilage defects of the knee. The first trial, a phase II, randomised, open label, multicentre dose-finding study in subjects with cartilage defects (4-10 cm^2) of the knee, has been detailed above. The analysis also included a Phase III, prospective, randomised, ongoing, multicentre clinical trial in subjects with smaller cartilage defects (1-3.99 cm^2) of the knee, which compares the efficacy and safety of Spherox with microfracture.

The pooled analysis used 12-month data, and it was conducted on three different populations: Safety population (127 participants), intention-to-treat population ([redacted] participants), and per protocol population [redacted] participants).

Changes in the KOOS total score and subscores from baseline (Day 0) to 12 months after implantation were estimated for the following subgroups (22):

- Defect size at implantation: 1 to < 4 cm^2, ≥ 4 to 10 cm^2
- Gender: male or female
- Age: 18–34 years, 35–50 years
- Localisation of defect: femur, patella
- Diagnosis: traumatic cartilage lesion, others, osteoarthritis, osteochondritis dissecans and femoral condyle location (medial or lateral).

Baseline characteristics

The baseline characteristics of patients in the pooled analysis are displayed in Table 33. The mean age of the patients in the pooled analysis safety population (N=127) was [redacted] years and the mean BMI [redacted] kg/m^2. Most patients were Caucasian ([redacted] and 4 patients were from other ethnic groups (Asian: [redacted] Black: [redacted] There were no major differences between the ITT and SAF populations in demographic variables.

Table 33. Demographic data of study patients (pooled analysis)

Population	SAF	ITT	PP
Age (years), mean ± SD	[redacted]	[redacted]	[redacted]
Height (cm), mean ± SD	[redacted]	[redacted]	[redacted]
Weight (kg), mean ± SD	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean ± SD range	[redacted]	[redacted]	[redacted]
Ethnicity (n (%)): Caucasian Asian Black	[redacted]	[redacted]	[redacted]

Table 34 provides an overview on the number of patients in each subgroup analysed in this pooled analysis by category and analysis population. The majority of the patients were male ([redacted] SAF). However age was well distributed, with approximately half the patients between 18 and 34 years old ([redacted] and [redacted] patients ([redacted] in the 35-50 years age group. The primary study defects were either localised on the femur or the patella. A defect location was not specified in [redacted] patients who did not undergo implantation.

Trauma was the most common cause for cartilage lesion ([redacted] SAF), whereas OA ([redacted] SAF) or OD ([redacted] SAF) were considerably less common diagnoses. Numerous less frequent individual diagnoses leading to cartilage lesions were combined into the category 'Others' ([redacted] SAF), which was similar in size to the trauma subgroup (22).

Table 34. Number of patients in each subgroup

Population n (%)		**SAF** *N = 127*	**ITT** *N = 121*	**PP** *N = 92*
Sex	female	[redacted]	[redacted]	[redacted]
	male	[redacted]	[redacted]	[redacted]
Age	18 - 34 years	[redacted]	[redacted]	[redacted]
	35 - 50 years	[redacted]	[redacted]	[redacted]
Defect size	1 - 3.99cm^2	[redacted]	[redacted]	[redacted]
	4 - 10cm^2	[redacted]	[redacted]	[redacted]
	Not specified	[redacted]	[redacted]	[redacted]
Defect localisation	Femur	[redacted]	[redacted]	[redacted]
	Patella	[redacted]	[redacted]	[redacted]
	Not specified	[redacted]	[redacted]	[redacted]
Femoral condyle	Medial	[redacted]	[redacted]	[redacted]
	Lateral	[redacted]	[redacted]	[redacted]
	Not specified	[redacted]	[redacted]	[redacted]
Diagnosis	Traumatic cartilage lesion	[redacted]	[redacted]	[redacted]
	Osteoarthritis (OA)	[redacted]	[redacted]	[redacted]
	Osteochrondritis dissecans (OD)	[redacted]	[redacted]	[redacted]
	Others	[redacted]	[redacted]	[redacted]

Efficacy results

The overall KOOS was calculated for the ITT (primary) by averaging the transformed sub scores. KOOS results ranged from 0–100, with lower values representing worse conditions. The KOOS results for the pooled analysis are displayed in Table 35.

In the ITT population, which was the primary analysis population of this pooled interim analysis, the KOOS overall score improved statistically significantly from [redacted] at baseline to [redacted] at 12 months (Visit 4) after implantation. This is a mean change of [redacted], with a p-value below [redacted]. A statistically significant increase in the overall KOOS was seen in all investigated subgroups, with the exception of the diagnosis subgroups 'OA' and 'OD'. Excluding these two subgroups, the mean improvements in the overall KOOS between baseline and Visit 4 were between 16.2 and 22.0 ($p \leq 0.0086$) in the other subgroups (22).

Table 35. Overall KOOS at each visit (pooled analysis, ITT)

Visit		Total *N = 121*
Values at each visit		
Pre-arthroscopy (baseline)	mean ± SD	[redacted]
Pre-implantation (Day 0')	mean ± SD	
Visit 1 (6 weeks)	mean ± SD	
Visit 2 (3 months)	mean ± SD	
Visit 2 (3 months)	mean ± SD	
Visit 3 (6 months)	mean ± SD	
Visit 4 (12 months)	mean ± SD	
Change from baseline		
Pre-implantation (Day 0')	mean ± SD	
Visit 1 (6 weeks)	mean ± SD	
Visit 2 (3 months)	mean ± SD	
Visit 3 (6 months)	mean ± SD	
Visit 4 (12 months)	mean ± SD	
	97.5% CI	
	p-value	

B.2.9 Indirect and mixed treatment comparisons

Results of the conducted indirect treatment comparison can be found below. See Appendix D for full details of the methodology.

B.2.9.1 Summary of the trials included in the indirect comparison

Three trials have been included in the indirect comparison: COWISI, SUMMIT and TIG/ACT. A summary of the main characteristics and outcomes used in the indirect comparison can be found in appendix D. Table 36 summarises the interventions included in each of the trials considered.

Table 36: Summary of the trials used to carry out the indirect treatment comparison

Study	Spherox	MF	MACI	ChondroCelect
COWISI (15)	Yes	Yes		
SUMMIT (23)		Yes	Yes	
TIG/ACT (24)		Yes		Yes

Reason for exclusion of additional studies identified during the systematic literature review can be found in **Error! Reference source not found.** (appendix D).

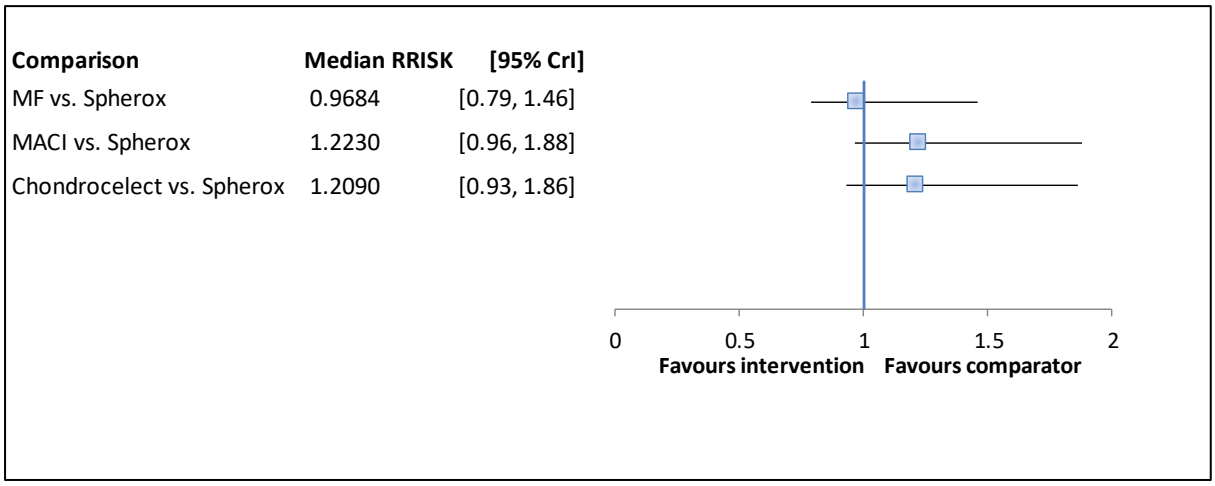
B.2.9.2 Results of the analysis

Two outcomes have been included and investigated in this NMA: number of responders; and failure rate. Results for each of the above outcomes can be found below. Due to the small number of trials informing each comparison in the network, there was not enough evidence to reliably inform the heterogeneity parameter in the random effects model. Therefore, only results derived from the fixed effects model will be presented.

Number of responders:

Figure 12 show the base case results for the 'number of responders' assuming Spherox as baseline treatment. The median RRs suggest that Spherox is associated with a higher number of responders when compared to MF and with a lower number of responders when compared to MACI and ChondroCelect. However, these results were not statistically significant with the 95% CrI crossing unity.

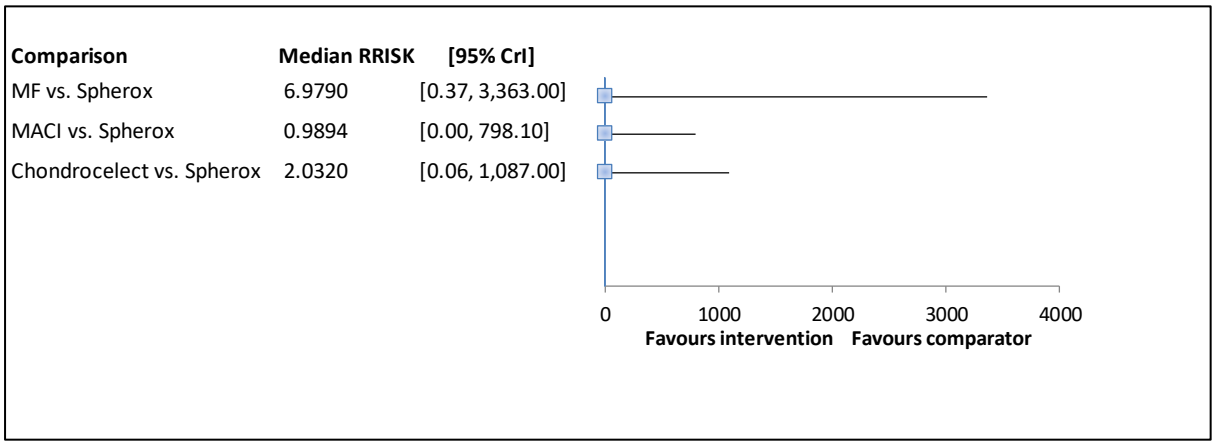
Figure 12: Forest plot for number of responders



Failure rate:

Figure 13 show the base case results for the 'failure rate' assuming Spherox as baseline treatment. The median RRs suggest that Spherox is associated with a lower failure rate when compared to MF and ChondroCelect and with a same number of failures when compared to MACI (no failures were observed in COWISI and SUMMIT). However, these results were not statistically significant with the 95% CrI crossing unity.

Figure 13: Forest plot for failure rate



B.2.9.3 Heterogeneity assessment

The key characteristics of the studies assessed for inclusion in the NMA are provided in **Error! Reference source not found.**-**Error! Reference source not found.** (appendix D).

The following sources of between-study heterogeneity were considered:

1. Trial design: inclusion/exclusion criteria, sample sizes, outcomes definition, length of follow up
2. Patient characteristics: lesion size, age at baseline, baseline KOOS

Trial designs and patient characteristics were compared to COWISI for the purposes of assessing heterogeneity. Tables summarising and comparing the three studies included can be found in appendix D.

Trial design – heterogeneity assessment

Inclusion criteria

There were some differences in inclusion criteria across the three studies. In particular, the SUMMIT trial included patients with moderate to severe KOOS pain value (<55) at baseline, which resulted in a study population with a lower baseline quality of life compared to COWISI and TIG/ACT. This additional inclusion criterion could have determined the difference in treatment effects observed. Another difference observed refers to the lesion size. In the SUMMIT trial, patients had to have a minimum lesion size of 3cm^2 to be enrolled.

Exclusion criteria

Exclusion criteria were similar across the included studies.

Sample size

There were differences in the sample sizes of the studies. However, sample size of all the trials included is very small, ranging from 50 to 72 patients per arm. With small sample sizes there is a risk of undermining the internal and external validity of a study.

Length of follow up

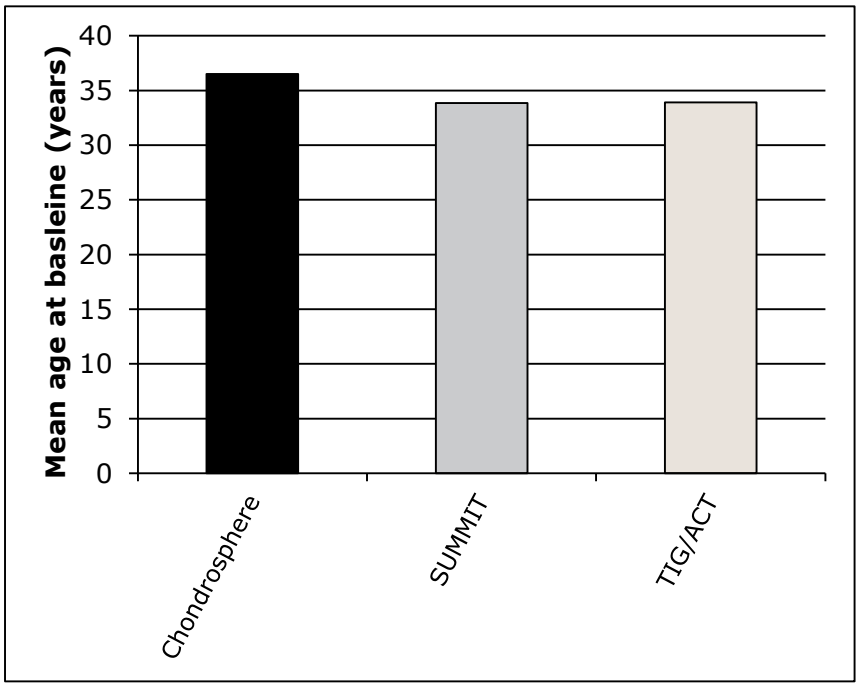
There were differences in the length of follow up used to populate these analyses. Both COWISI and SUMMIT published results of interest (number of responders and failure rate) at 2 years, while TIG/ACT only published the two outcomes at 3 years.

Patient characteristics – heterogeneity assessment

Mean age at baseline

There is some evidence to suggest that younger patients may have a better response compared to older patients (32). However, the included studies were comparable with a mean baseline age across studies ranging from 32.9 to 37.0 years.

Figure 14 Patients baseline characteristics (mean age)



Outcome definition:

The way in which outcomes are defined in the included trials represent one of the most relevant aspect to be considered while interpreting and comparing the results.

- Treatment failure: across all the included trials, treatment failure was defined as the need for revision surgery, therefore no issues in comparing the results were identified

- Responders: definition of responders varies across all the trails included in this indirect comparison, and this makes the results very difficult to compare. Each trial definition is summarised below:

  COWISI: A responder was defined as having at least a 10-point improvement in the overall KOOS scale;

  SUMMIT: A responder was defined as having at least a 10-point improvement in both the KOOS pain and function subscales

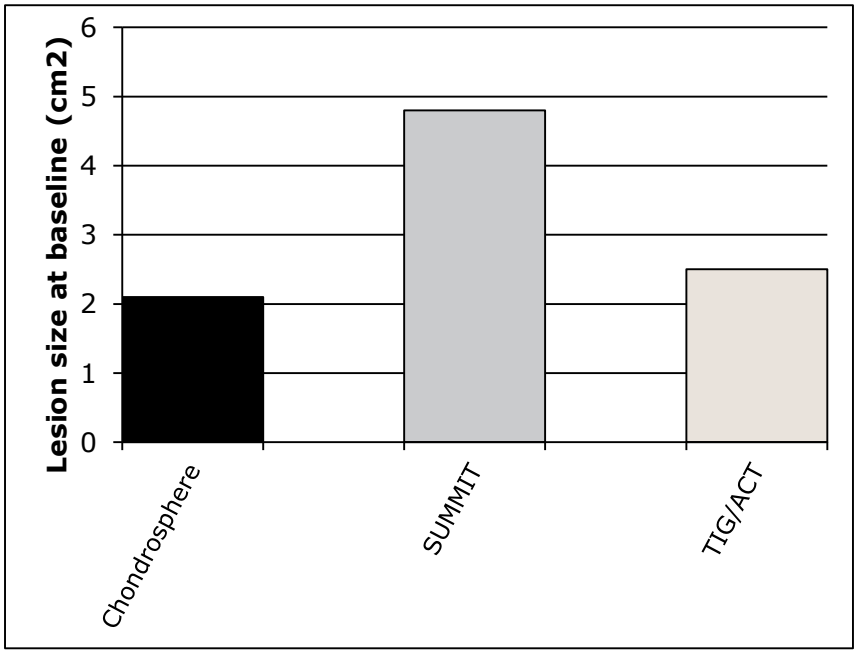
  TIG/ACT: A responder was defined as having an increase from baseline in overall KOOS of at least 10 percentage points and/or an increase from baseline

of at least 10 percentage points in at least 3 of the 4 KOOS subdomains and/or an improvement from baseline in the degree of knee disorder severity of at least one category or a decrease from baseline of at least 20 percentage points in VAS pain score and/or an improvement in the degree of knee disorder severity of at least one category.

Lesion size

Lesion size differ across studies. Mean lesion sizes were <2.5 cm^2 in COWISI and TIG/ACT trials and more than 4cm^2 in the SUMMIT trial. There is some evidence to suggest that ACI produces better results than MF in larger lesions.

Figure 15 Patient baseline characteristics (lesion size)



Baseline KOOS score

Baseline KOOS score differ across studies even in the way it is reported. COWISI and TIG/ACT trials report an overall KOOS score while the SUMMIT trial reports the score split between pain and functional subscale. In the COWISI trial an imbalance between arms in terms of baseline KOOS score is observed (56.6 vs. 51.7) (**Error! Reference source not found.**). In the SUMMIT trial, patients reported a significant lower baseline levels in all 5 KOOS subscores compared to patients in the COWISI trial (Table 37).

Table 37: Baseline KOOS: COWISI and SUMMIT

	COWISI (15)		SUMMIT (23)	
	Baseline value (Day before arthroscopy)			
	Spherox	Microfracture	MACI	Microfracture
KOOS Overall	**56.6 ± 15.4**	**51.7 ± 16.5**		
Pain	[redacted]	[redacted]	37.0 ± 13.5	35.5 ± 12.1
symptoms	[redacted]	[redacted]	48.3 ± 16.9	44.4 ± 18.6
activities in daily living	[redacted]	[redacted]	43.5 ± 18.2	42.6 ± 19.6
function in sport and recreation	[redacted]	[redacted]	14.9 ± 14.7	12.6 ± 16.7
quality of life	[redacted]	[redacted]	18.8 ± 14.7	17.2 ± 14.1

At the end of the 24th month, patients receiving Spherox and MACI report similar results in all the 5 KOOS subscores however, micro fracture patients in the COWISI trial reported better results than those in the SUMMIT trial (Table 38). This difference can only be explained by the lower KOOS at baseline for patients in the SUMMIT trial and by chance due to the small sample size.

Table 38: 24-month KOOS: COWISI and SUMMIT

	COWISI (15)		SUMMIT (23)	
	24 months			
	Spherox	Microfracture	MACI	Microfracture
Pain	[redacted]	[redacted]	82.5 ± 16.2	70.9 ± 24.2
symptoms	[redacted]	[redacted]	83.7 ± 14.0	72.7 ± 19.5
activities in daily living	[redacted]	[redacted]	87.2 ± 16.5	75.8 ± 24.2
function in sport and recreation	[redacted]	[redacted]	60.9 ± 27.8	48.7 ± 30.3
quality of life	[redacted]	[redacted]	56.2 ± 23.9	47.3 ± 27.0

Uncertainties in the indirect and mixed treatment comparisons

The main uncertainty identified relates to the comparability of the trials. Trials differ in patient characteristics as well as outcome definition. These differences should be carefully considered while interpreting the results. Heterogeneity within and between trials could not be statistically addressed due to the small number of studies included.

B.2.10 Adverse reactions

B.2.10.1 Phase III trial

Safety analyses and assessments were conducted with all patients treated (safety population, n=102) (15). Adverse events were recorded by system organ class (SOC) and preferred term using MedDRA (Version 15.1) (15). The frequency and type of adverse events, vital signs, physical examination, concomitant pain medication, and laboratory values were analysed. Concomitant pain medications were listed as reported and summarised for each patient, presenting duration of use, number of different active agents, and quantity, if applicable (15).

Extent of exposure

Each patient in the Spherox group received a single, standard dose of Spherox (10–70 spheroids/cm^2); in [redacted] patients the doses were lower because of inadequate spheroid growth (Table 39). No product was used in patients treated by microfracture so estimates of exposure are not appropriate for that group (15).

Table 39. Exposure to the test product: Dose administered (safety population) [(15), p151, Table 55]

Measure of exposure		**Spherox group** *N* = 52	**Microfracture group** *N* = 50
Spheroids/cm^2 based on defect area as found by arthroscopy before debridement*	Mean ± SD	[redacted]	*not applicable*
	Median	28.5	
	Range	10 – 130	
Spheroids/cm^2 based on defect area as found at implantation, after debridement*	Mean ± SD	[redacted]	
	Median	[redacted]	
	Range	[redacted]	
Number of spheroids	Mean ± SD	[redacted]	
	Median	60	
	Range	12 – 175	

*Area at arthroscopy was used for determination of dose (amount of Spherox); area at implantation was post-debridement and therefore more accurate.

Summary of adverse events

Adverse events recorded in the trial up to the cut-off date for this analysis (20.02.2017) are summarised in Table 40. There were 132 and 121 reports of adverse events in the

Spherox and microfracture groups, respectively. There were no noticeable difference between the treatment groups with regard to the overall incidence of adverse events, the number of patients with any adverse events or the number of patients with "probably" or "possibly" treatment-related adverse events. There were, however, greater proportions of severe and serious adverse events in the microfracture arm. There were no fatal adverse events in either arm of the trial.

Table 40. Summary of adverse events (safety population) [(15), p144, Table 53]

	Spherox ***N* = 52**	**Microfracture** ***N* = 50**
Any adverse event (Nos. of patients)	[redacted]	[redacted]
Any treatment-related adverse event	[redacted]	[redacted]
Any severe adverse event	[redacted]	[redacted]
Any serious adverse event	[redacted]	[redacted]
Any adverse event (Nos. of events)	[redacted]	[redacted]
Any treatment-related adverse event (Nos. of events)	[redacted]	[redacted]

No adverse events led to premature withdrawal from the trial in the Spherox group; in the microfracture group, [redacted] patients withdrew due to adverse events. The withdrawals were due to [redacted] events in [redacted] patients. No adverse events led to permanent sequelae in the Spherox group, but an adverse event leading to permanent sequelae was recorded for one patient in the microfracture group (15).

Adverse events by MedDRA SOC and preferred term

A summary of the adverse events recorded in the trial, showing both the numbers of reported events (n_E) and the numbers of patients affected (n_P), is provided in Table 41. Numbers of adverse events, and of patients affected, in the various SOCs were similar in each treatment group. "Musculoskeletal and connective-tissue disorders" was the SOC most often affected; this was anticipated due to the nature of the trial procedures. Adverse events in other SOCs were less frequent. Patients with "metabolism and nutrition disorders", were slightly more common in the Spherox group (n = [redacted]) than in the microfracture group (n = [redacted]); the individual events were hypertriglyceridaemia and hyperlipidaemia and are unlikely to be associated with the Spherox treatment (15).

Table 41. Adverse events by MedDRA SOC and preferred term (safety population) [(15), p153, Table 57]

	Spherox *N* = 52		Microfracture *N* = 50	
	n_P (%)	n_E	n_P (%)	n_E
Any SOC	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective-tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Joint effusion	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Joint swelling	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Post-traumatic pain	[redacted]	[redacted]	[redacted]	[redacted]
Joint dislocation	[redacted]	[redacted]	[redacted]	[redacted]
Ligament rupture	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and admin, site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic-system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Bone-marrow oedema	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous disorders	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]

Numbers of patients (n_P) and events (n_E) are given. Cut-off ≥3 patients overall (adverse events recorded for only 1 or 2 patients overall are not included). Patients with more than one adverse event in a given category are counted only once. The SOCs and, within each SOC the preferred terms, are shown in descending order of nP overall.

Relationship of adverse events to the study treatment

The incidences of individual adverse events considered to be related to treatment, and the corresponding SOCs were similar in each treatment group. All adverse events that were considered “possibly” or “probably” related to the study treatment are shown in

Table 42. Treatment-related arthralgia, joint effusion, and joint swelling affected the greatest number of patients, and expected based on the surgical procedure.

An analysis of the “musculoskeletal and connective-tissue disorders” SOC, including the investigator’s assessment of the likelihood of a causal link between the adverse event and the study treatment, revealed a greater number of adverse events in the Spherox group (n = [redacted]) than in the microfracture group (n = [redacted]). A higher percentage of events were considered treatment-related in the microfracture group ([redacted]) than in the Spherox group ([redacted]). Few cases—particularly of joint effusion, joint swelling and arthralgia—were considered by the investigator to be unrelated to the study treatment (Table 43) (15).

Table 42. Adverse events classified as probably or possibly related to the study treatment, by MedDRA SOC and preferred term (safety population) [(15), p155, Table 58]

	Spherox *N* = 52		**Microfracture** *N* = 50	
	n_P (%)	n_E	n_P (%)	n_E
Any SOC	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective-tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Joint effusion	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Joint swelling	[redacted]	[redacted]	[redacted]	[redacted]
Synovial cyst	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Chondromalacia	[redacted]	[redacted]	[redacted]	[redacted]
Joint adhesion	[redacted]	[redacted]	[redacted]	[redacted]
Joint instability	[redacted]	[redacted]	[redacted]	[redacted]
Muscle contracture	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]
Tendonitis	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]	[redacted]
Epicondylitis	[redacted]	[redacted]	[redacted]	[redacted]
Suture-related complication	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and admin, site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic-system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Bone-marrow oedema	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous disorders	[redacted]	[redacted]	[redacted]	[redacted]
Scar pain	[redacted]	[redacted]	[redacted]	[redacted]
Skin discolouration	[redacted]	[redacted]	[redacted]	[redacted]
Skin dystrophy	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Immune-system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]

Numbers of patients (n_P) and events (n_E) are given.

Table 43. Adverse events in the SOC "musculoskeletal and connective-tissue disorders" and their relationship to the study treatment, by treatment group (safety population) [(15), p156, Table 59]

	Spherox *N* = 52				**Microfracture** *N* = 50			
Relationship:	NR	Unl	Pos	Pro	NR	Unl	Pos	Pro
Any adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chondromalacia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint instability	[redacted]	[redacted]	[redacted]	[redacted]				
Tendonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bursitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cervical spine flattening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint adhesion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle contracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle tightness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Synovial cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tendon discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tendon disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Numbers of patients are given. NR, not related; Unl, unlikely to be related; Pos, possibly related; Pro, probably related.

B.2.10.2 Phase II trial

There were no fatal adverse events in this trial. In the first year after treatment, [redacted] serious adverse events (convulsions and arthralgia) were judged unrelated to the study treatment. In the second year, [redacted] further serious adverse events occurred: syncope (medium-dose group, unrelated), umbilical hernia (high-dose group, unrelated), meniscus lesion (low-dose group, unrelated) and [redacted] episodes of chondropathy in the same patient (high-dose group, probably related). In the third year, [redacted] further serious adverse events occurred: [redacted] of chondropathy (low-dose group, unlikely to be treatment related, and medium-dose group, unrelated), [redacted] of arthralgia (low-dose group, probably related, and high-dose group, unrelated) and uterine cyst (low-dose group, unrelated). No adverse events led to any patient's withdrawal from the study.

In summary, adverse events were as follows (numbers of patients are shown, except in the bottom row; m = months):

Table 44: Adverse event in the trial

Dose group:	Low N = [redacted]		Medium N = [redacted]		High N = [redacted]		All N = [redacted]	
Time after treatment:	12m	48m	12m	48m	12m	48m	12m	48m
Any adverse event	[redacted]							
Any treatment-related adverse event	[redacted]							
Any severe adverse event	[redacted]							
Any serious adverse event	[redacted]							
Number of events	[redacted]							
Number of treatment-related events	[redacted]							

Most of the patients in all dose groups reported at least one adverse event. At the 12-month assessment the numbers of reports had no clear relationship with dose level (see table above); at the 24-month, 36-month and 48-month assessments there were rather more adverse events in the high dose group; however, the incidence of treatment-related adverse events was not greater in this group compared with the other groups. Adverse events in the System Organ Class (SOC) 'musculoskeletal and connective-tissue disorders' were the most frequent, especially joint effusion; this is regarded as being related to the surgical procedure. Almost all cases of joint effusion occurred within the first year after study treatment. Adverse events in other SOCs were less frequent, most occurring only once.

No dose relationship could be observed regarding onset, duration or severity of adverse events.

The laboratory measurements (haematology and clinical chemistry), the assessments of vital signs, the electrocardiography, the measurements of body weight and the recorded concomitant medications gave no indication of any unwanted effect of the trial treatment, while the patients' use of pain medication at Visit 2 (12 weeks after implantation) and thereafter was consistent with a long-term advantage of the treatment in all treatment groups (16).

B.2.11 Ongoing studies

There are no ongoing RCTs of Spherox in patients with cartilage defects of the knee from which additional evidence is likely to be available in the next 12 months.

B.2.12 Innovation

Spherox is a fourth generation ACI and represents a marked improvement over micro fracture (MF) and the other autologous chondrocyte implantations available:

Comparison with MF

Spherox demonstrates the following improvements over MF:

- Spherox aims to produce hyaline-like cartilage whereas MF is associated with the production of fibrocartilage which is inferior cartilage
- Spherox is shown to be more effective than MF across age categories studied
- Spherox can be used for large defects (up to 10 cm^2) whereas MF is generally used on smaller defects (1-4cm^2)
- Spherox is associated with fewer serious adverse effects than MF
- Spherox may reduce the following complications because of the autologous cells used in the procedure:
    - Rejection and incompatibilities – where patients may require further procedures
    - Viral contaminations
    - Overcomes any objections to the procedure on religious grounds - no porcine derived collagen membrane
- Using Spherox as first line surgical treatment before MF could be more effective than using MF 1st line before Spherox (25)

Comparison with other ACIs

The following improvements can be associated to Spherox when compared to other ACIs:

- Spherox can be implanted via an arthroscopy or mini-arthrotomy whereas other ACIs require arthrotomy for implantation. Spherox requires a shorter, simpler and less invasive treatment compared to conventional ACIs. This results in:
    - Lower procedural costs
    - Less resource use
    - Reduction in theatre time and costs
    - Reduced rehabilitation
    - Quicker return to improved quality of life
- Spherox is a 4th generation autologous product whereas traditional ACIs are 3rd generation. Key difference being in the application that 3rd generation uses seeded scaffolding and 4th generation cultivates a membrane
- Spherox overcomes any objections to the procedure on religious grounds, as there is no animal derived collagen membrane
- Spherox can be used in defect sizes up to 10cm^2, whereas some ACIs (ChondroCelect) can be used only in defect sizes 1-5cm^2
- Spherox costs less than other ACIs (MACI and ChondroCelect)

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Efficacy summary

The primary analysis, performed with the ITT1 population, followed the prospectively defined hierarchical scheme.

In the primary analysis, in the assessment of “overall KOOS” for the ITT1 population, both Spherox and microfracture yielded statistically significant improvements relative to baseline (Step 1). For the patients treated with Spherox the mean overall KOOS score rose from 56.6 ± 15.4 at baseline to 78.7 ± 18.6 at Visit 4 (12 months) and to [redacted] at Visit 6 (24 months), while for those treated by microfracture the score rose to 51.7 ± 16.5 to 68.1 ± 18.6 after 12 months and [redacted] after 24 months ($p < 0.0001$ for all) (15).

According to the between-group primary analysis conducted for the 24-month results the Spherox treatment passed the test of significant non-inferiority compared with microfracture; thus the primary goal of the study was achieved. Repetition of the primary analysis with different study populations (PP, ITT2, observed cases) gave similar results.

The KOOS subscores yielded the same qualitative result as the full-KOOS analysis, i.e., for each of these non-inferiority was demonstrated, and in one case (subscore ‘function in daily living’) the threshold for superiority was passed. Although improvements with respect to baseline were in each case greater for the Spherox than for the microfracture group. [redacted] for the Overall KOOS with descriptive statistical significance. “Function in sport and recreation”, “function in daily living”, and “knee-related quality of life” decreased between the pre-treatment assessments and the first post-treatment assessment (Visit 1, 6 weeks after the study treatment) and then rose during the study to higher than pre-treatment values.

The results for all other secondary variables supported those of the KOOS analyses. The overall MOCART score showed improvements from Visit 2 to Visit 4 (3 to 12 months) with a further improvement to Visit 6 (24 months) in both treatment groups. The MOCART score was 67 for the Spherox group and 62 for the microfracture group

at Visit 2, improving respectively to [redacted] at Visit 4 and to [redacted] at Visit 6. The slightly better result for the Spherox group should, however, be interpreted with caution as no baseline MOCART scores were available for comparison. The individual MOCART items showed variable differences with regard to treatment response and also to the difference between treatment groups. The greatest improvements were observed in 1 (defect repair), 3 (surface), 5 (signal intensity), 7 (subchondral bone), and 9 (synovitis). A systematic difference between the two treatment groups could not be established.

The IKDC assessments and the Modified Lysholm score showed comparable improvements in both treatment groups; the improvement was generally slightly greater in the Spherox group baseline and Visit 4 (12 months), with a smaller difference at Visit 6 (24 months).

In the indirect comparison, Spherox was associated with numerically better response and failure rate compared to MF but numerically lower results when compared to the other ACIs. However, none of the results were statistically significant with the CIs crossing 1. In addition, there was a high level of heterogeneity across several aspects of the trials included in the analyses, and this makes the results difficult to interpreted and generalised in clinical practice.

B.2.13.2 Safety summary

In general, patient exposure to Spherox in the Spherox group was as planned. The dose range was 6–70 spheroids/cm^2 (absolute total dose 12–175 spheroids. Two patients received lower doses than the standard dose of 10–70 spheroids per cm^2 because of inadequate spheroid growth, however, all patients in the Spherox group received a sufficient dose to permit a meaningful assessment of the safety of Spherox (15).

The overall incidence of adverse events, and of patients affected, in the various SOCs differed little between the two treatment groups ([redacted]% of patients in the Spherox group and [redacted]% in the microfracture group). The overall incidence of adverse events, and numbers of patients affected, in the various SOCs were not notable and did not differ between the two treatment groups. As expected, considering the nature of the study

procedures, the SOC most often affected was “musculoskeletal and connective-tissue disorders” ([redacted] of patients in the Spherox group, [redacted] in the microfracture group). Adverse events in other SOCs were considerably less frequent, and most occurred only once up to Visit 6 (24 months). There were no clear differences between the two treatment groups regarding the incidence of adverse events and of the SOC classes in which they were grouped (15).

Six of the 14 severe adverse events in the microfracture group (skin dystrophy, nausea, bone-marrow oedema in two patients, arthralgia, and joint swelling) were considered probably treatment-related. Serious adverse events (n = [redacted]) were less frequent in the Spherox group (n=[redacted]) vs. [redacted] serious events in the microfracture group. All four SAE in der Spherox group were considered unrelated to treatment. All except two of these adverse events resolved (Hodgkin’s disease [Spherox, unrelated] and arthralgia [microfracture, possibly treatment related]) (15).

No patients died during the study. In the Spherox group[redacted] non-fatal serious adverse events were recorded (abdominal neoplasm, cystitis, Hodgkin’s disease, and malaise) compared with [redacted] in the microfracture group (deep vein thrombosis, meniscus lesion, joint adhesion, arthralgia, cellulitis, and cartilage injury). Although there is no relationship between events occurring in the microfracture group and the study product, it must be considered that the deep vein thrombosis could have been promoted by post-operative immobilisation and that the pre-existing meniscus lesion could have been exacerbated by the operation (15).

Adverse events considered to be “possibly” or “probably” related to the study treatment were mainly in the “musculoskeletal and connective-tissue disorders” SOC (Spherox group [redacted], microfracture group [redacted] of patients). No relevant differences in treatment-related adverse events between the groups were observed (15).

Laboratory measurements, assessments of vital signs, electrocardiography and other observations related to safety did not reveal signs of any possible harmful effects of Spherox treatment.

In summary, the adverse-event pattern of Spherox in this study accorded with the known adverse-event profile of Spherox as set out in the Investigator's Brochure. The

laboratory and vital-signs measurements, electrocardiography, body weight, and concomitant medications did not reveal any harmful effect of the treatment with Spherox (15).

B.2.13.3 Overall conclusions

Phase III trial data shows that Spherox was at least as good as that of the microfracture treatment across all criteria, and for some efficacy measures was better. In the first year after treatment, patients in the Spherox group improved more quickly than those in the microfracture group. A greater improvement was seen in the microfracture group during the second year. The primary statistical analysis at 12 and 24 months after treatment confirmed the non-inferiority of Spherox compared with microfracture. The two treatments had largely similar adverse event profiles. No unwanted effects of the study treatment were observed during examinations of other safety variables during the study.

[redacted] at the descriptive level did not reveal statistical significance for the [redacted], though narrowly missed. It should however be noted that the study was powered for non-inferiority, not for superiority. The KOOS subscores yielded the same qualitative result as the full-KOOS analysis, i.e., for each of these non-inferiority was demonstrated, and in one case (subscore 'function in daily living') the threshold for superiority was passed. Additional (post hoc) efficacy analysis conducted, supported the non-inferiority and established superiority of the Spherox treatment compared with microfracture at two years.

An indirect comparison found that, compared with other ACIs, there are no statistically significant differences versus Spherox and so these treatments could be considered of similar efficacy. However, the results from the indirect comparison should be interpreted with caution given the high level of heterogeneity across the trials included.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

The systematic literature review for cost-effectiveness studies involving the intervention and/or comparators is detailed in Appendix G.

A summary of eight publications included is presented in Table 45. One was a cost-effectiveness analysis by Miller et al (26), one was a costing study by Zhang et al (27) and six were cost-utility analyses by Clar et al (28), Derrett et al (29), Elvidge et al (30), Gerlier et al (31), Mistry et al (32) and Samuelson and Brown (33). Six studies used a decision-analytic modelling approach; Clar et al, Elvidge et al and Mistry et al used a Markov model structure while Gerlier et al, Miller et al and Samuelson and Brown used a decision tree model structure. Gerlier et al employed two time horizons of 5 and 40 years to model the short-term clinical success and the long-term effectiveness of the treatment. Both Miller et al and Samuelson and Brown employed a time horizon of 10 years. A Markov model structure was provided by Clar et al for the evaluation of long-term cost-effectiveness of treatment with 16 health states and a 50-year time horizon. Both Elvidge et al and Mistry et al utilised a lifetime horizon for the Markov model and included 15 and 11 health states respectively. Two studies did not use a modelling approach; Derrett et al assessed cost-effectiveness by performing a hospital-based cross-sectional study. General health status (EQ-5D), cost and resources use were collected to two years after the intervention. Zhang et al performed a retrospective review of one-year preoperative and one-year postoperative costs associated with MF, OAT, OC allograft and ACI using a national private insurance database (PearlDiver).

Table 45. Summary of published cost-effectiveness studies

Study	Summary of model/ analysis	Patient Population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	Base case results (ICER or cost-benefit)
Clar et al (28)	A Markov model to evaluate the cost-effectiveness of ACI versus MF and mosaicplasty from the NHS perspective. The analysis consists of a short-term, a medium-term and a long-term modelling. The long-term model consists of 16 health states and a 50-year time horizon. Effectiveness data were taken from the literature; the cost data were taken from Aberdeen Royal Infirmary and the Verigen submission.	Patients with symptomatic cartilage lesions	• Debridement: 1785.9 • MF: 1901.2 • ACI: 1957.6 • Mosaicplasty: 1881.3	• Debridement: £666,025 • MF: £767,620 • ACI: £971,413 • Mosaicplasty: £ 1,037,025	• MF: £881 per QALY • ACI: £3,617 per QALY • Mosaicplasty: dominated
Derrett et al (29)	A UK-based retrospective study to evaluate the cost-effectiveness of ACI versus mosaicplasty two year after interventions. The ICER of ACI compared to mosaicplasty was found to be within the NHS WTP threshold of £30,000 per QALY. The model design was not reported. The QoL, cost and healthcare resource use data were collected at two year post intervention.	Patients who received first ACI or first mosaicplasty for chondral or osteochondral lesions of 1 cm diameter or more at the Royal National Orthopaedic Hospital (RNOH) between March 1997 and February 2001. Patients on the ACI waiting list was also included. Patient group and numbers: • 53 ACI recipients • 20 mosaicplasty recipients 22 ACI WL recipients	• ACI: 0.46 • Mosaicplasty: 0.12	• ACI: £10,600 • Mosaicplasty: £7948	£16,349/QALY
Elvidge et al (30)	A Markov model to evaluate the cost-effectiveness of ChondroCelectversus MF from the NHS perspective. The model consists of 15	Adult patients < 50 years of age with symptomatic cartilage	• ChondroCelect: 16.57 • MF: 15.85	• ChondroCelect: £23,307 • MF: £8008	£21,245/ QALY

Study	Summary of model/ analysis	Patient Population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	Base case results (ICER or cost-benefit)
	health states and have a lifetime horizon. The effectiveness data were collected from TIG/ACT phase III trial. EQ-5D data were mapped from the SF-36 data collected during the trial. Cost and healthcare resource use data were taken from NHS reference costs, inputs from the NICE appraisal process and previous HTA review by Clar et al (28).	lesions of the femoral condyles who had not developed OA.			
Gerlier et al (31)	A cost-utility with a decision tree to evaluate the cost-effectiveness of ChondroCelectagainst MF from a healthcare payer perspective over a 40-year horizon. The effectiveness data were collected from the TIG/ACT phase III trial. The cost and healthcare resource use data were collected from the Belgium National Institute for Health and Disability Insurance website, All Patients Refined Diagnosis Related Group and Belgium pharmacoeconomic guidelines. The QoL data were derived from the SF-36 questionnaires collected during the trial.	Adult patients aged<50 years with symptomatic cartilage lesions of the femoral condyles who had not yet developed OA	• ChondroCelect: 21.08 • MF: 19.79	• ChondroCelect: €29808 • MF: €9006	€16,229 per QALY

Study	Summary of model/ analysis	Patient Population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	Base case results (ICER or cost-benefit)
Miller et al (26)	A decision tree to evaluate the cost-effectiveness of MF and OAT for the treatment of isolated articular cartilage lesions of the distal femur over a 10-year horizon. Cost data were collected from the authors' academic institution. Effectiveness data were collected from literature.	Adult patients with articular cartilage lesions of the distal femur.	N/A	Total net procedure costs in 1 and 10 years respectively: • MF: $8769 & $10,483 OAT: $10,612 & $11,479	Costs per point (outcomes scores) improvement. • Lysholm: MF: $339 OAT: $469 • Tegner: MF: $4558 OAT: $4415 • HSS: MF: $1118 OAT: $1213 • ICRS: MF: $407 OAT: $309
Mistry et al (32)	A Markov model was used to evaluate the cost-effectiveness of ACI against MF for patients with symptomatic articular defects of the knee from the NHS perspective over a lifetime horizon. QoL data were derived primarily from Gerlier et al (31). Cost data were collected from NHS reference costs and the previous HTA review by Clar et al (28). Healthcare resource data were based on clinical experience.	Patients with symptomatic articular cartilage defects of the knee with a starting age of 33 years	Scenario 1: Patients all receive ACI as secondary repair after primary repair • ACI: 18.0228 • MF: 17.0284 Scenario 2: Patients all receive MF as secondary repair after primary repair • ACI: 17.0033 • MF: 17.9570	Scenario 1: • ACI: £20,921 • MF: £6617 Scenario 2: • ACI: £19,892 • MF: £5015	Scenario 1: £14,395/QALY Scenario 2: £15,598/QALY

Study	Summary of model/ analysis	Patient Population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	Base case results (ICER or cost-benefit)
Samuelson and Brown (33)	A cost-utility study with a decision tree to evaluate the cost-effectiveness of ACI-C versus ACI-P with a 10-year horizon. The model considered treatment failure and graft hypertrophy. The clinical effectiveness and QoL data were derived from literature. The cost data were collected from a local orthopaedic speciality hospital.	Adult patients (30 years of age) with a focal chondral injury that satisfies the conditions for ACI repair	Not stated	• ACI-C: $66,940 • ACI-P: $66,752	Costs per QALY ACI-C: $9243 ACI-P: $9466
Zhang et al (27)	A cost study to evaluate the perioperative management of articular cartilage lesions in the US. The cost data were collected using a national private insurance database (PearlDiver).	All patients who underwent a cartilage repair procedure between 2008 and 2010 in USA	N/A	Consolidated overall perioperative and surgical costs PPAC (per-patient average charge): ACI: $16,016.70 (highest) MF: $7,258.51 (lowest)	N/A

B.3.2 Economic analysis

The results of the search for relevant cost-effectiveness studies showed that the majority of studies in treatment for articular cartilage defects in the knee used a decision-analytic modelling approach. The most relevant study was conducted by Mistry et al (32), which was an economic evaluation undertaken to update NICE guidance in this therapeutic area and assessed all comparator technologies included in this submission. The analysis did not include the intervention technology, Spherox, therefore a *de novo* economic model was developed to assess the cost-effectiveness of Spherox versus relevant comparators.

Mistry et al used an 11 health-state Markov model structure extrapolated over a lifetime horizon. For consistency and comparability, we adopted the approach taken by Mistry et al for the development of this *de novo* model. The model and analysis are further described below. A summary of the previous appraisal (10), Mistry et al, and this appraisal is presented in Table 46.

Table 46 Features of the economic analysis

	Previous appraisals	**HTA report**	**Current submitted model**	
Factor	**TA89 (10)**	**Mistry et al (32)**	**Chosen values**	**Justification**
Time horizon	10 years for both short-term model and medium-term model; 50 years for long-term model	Lifetime	Lifetime	Time horizon has to be sufficiently long to capture potential, relevant costs and benefits experienced over the long-term (from initial repair to knee replacement)
Effect beyond the duration of the trial evidence	Assumptions: • Any treatment that gives 100% hyaline cartilage will prevent later osteoarthritis and knee replacement • All injured knees with fibrocartilage will develop osteoarthritis over time • Success rates after each procedure: - ACI: 85% success (95% CI 76 to 94) Peterson et al (34) - MF: 80% success (95% CI 71 to 89) Steadman et al (35) - Mosaicplasty: 90% success (95% CI 88 to 92) Hangody et al (36)	• Transition probabilities remained the same beyond the duration (2-year) of the trial evidence • The timing of knee replacement was based on data from the RCT comparing ACI against MF by Knutsen et al (37) • Utility of patients who had successful MF repair after 5 years: 0.654 • Utility of patients with successful ACI repair after initial MF repair after 4 years: 0.789	• Transition probabilities remained the same beyond the duration (2-year) of the trial evidence • The timing of knee replacement was based on data from the RCT comparing ACI against MF by Knutsen et al (37) • Utility of patients who had successful MF repair after 5 years: 0.654 • Utility of patients with successful ACI repair after initial MF repair after 4 years: 0.789 • Annual ACI failure rate of 1.25% after 2 years (beyond trial)	While transition probabilities remain the same in the model, the effects beyond the duration of the trial were reflected on the utility values. For this to work we made three assumptions: 1. For patients stay in the same successful repair health states after MF from year 5 and onwards, the utility would fall to the same as that of pre-operation because the benefit of MF declines after 5 years. 2. As ACI is less effective in patients who had prior MF, we assume that the utility of patients undergoing ACI after initial MF after 4 years and plus was the average of utilities of those who had clinical success and those who had no clinical success after 5 years following ACIs. 3. We assumed that MACI and Spherox will have an annual failure rate of 1.25% after 2 years

Source of utilities	A HRQoL literature search was conducted however no included studies were suitable for the appraisal. Therefore an assumption of an incremental QoL (0.1) after successful intervention was made.	Gerlier et al (31) supplemented by Jansson and Granath (38), Dong and Buxton (39) for knee replacement	Gerlier et al supplemented by Jansson and Granath, Dong and Buxton for knee replacement	Gerlier et al compared ACI with MF using data from the TIG/ACT ChondroCelect trial, with EQ-5D scores derived from the SF-36 and KOOS measures. Due to the sequence of treatment considered in the Markov model, additional utility data was adopted from relevant studies.
Source of costs	Aberdeen Royal Infirmary: costs of surgery, days as an inpatient and follow-up physiology (28) Verigen submission: costs of cell culture in ACI (28)	Costs of MACI and ChondroCelect cell culture were UK list price. Costs of surgical procedure, MF, and further TKR were obtained from Clar et al and inflated to 2012-13 prices using the HCHS index. Costs of first knee replacement (TKR) and post-surgery costs including outpatient visits and rehab visits were obtained from 2012-13 NHS reference costs (32).	Costs of Spherox, MACI and ChondroCelect cell cultures were based on UK list prices. Surgical procedure costs, and costs of MF were obtained from Mistry et al (32) inflated to 2015-16 prices using the HCHS index (40). First knee replacement costs were obtained from 'National Prices and National Tariff 2016/17' (41). Costs of further knee replacement (TKR) and post-surgery costs including outpatient visits and rehab visits were obtained from 2015-16 NHS reference costs (42).	The most updated NHS reference costs or national tariff costs were sought. When data was not available, related costs were obtained from Mistry et al (32) and inflated to 2015/16 costs using the HCHS index.

Patient population

Per the final scope from NICE, the population is adults with articular cartilage defects in the knee.

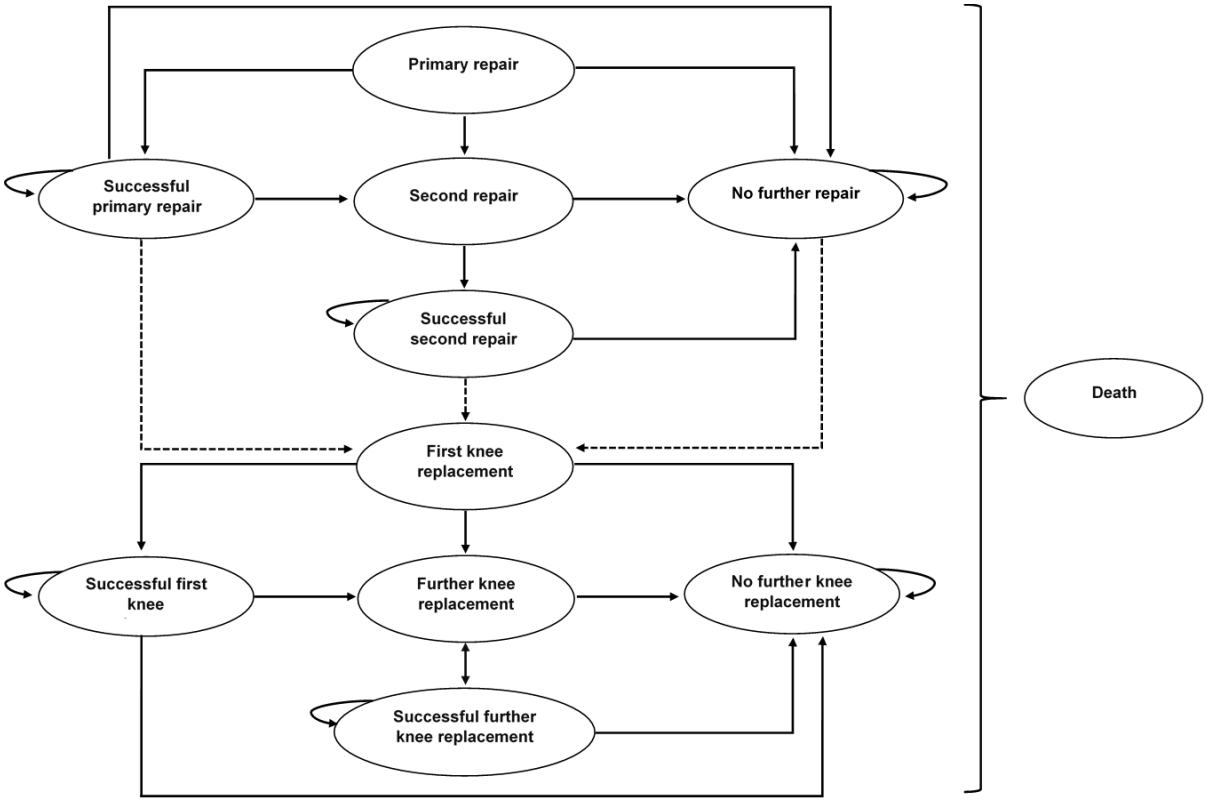
Model structure

The model was developed in Microsoft Excel to compare Spherox to MF, MACI and ChondroCelect. A model structure similar to the structure described in Mistry et al (32) was created which reflects different clinical pathways for patients with symptomatic articular cartilage defects of the knee. The Markov structure is presented in Figure 16.

All patients enter the model and receive a primary repair, then move through states of success (successful primary repair) or failure (secondary repair) or no further repair. Following second repair, patients can move to a successful state (successful secondary repair) or no further repair state. Patients transition through these five states until age 55. Patients can also experience death from any state at any time in the model.

At age 55, patients are eligible to transit to additional states to experience knee replacements. The first knee replacement can be partial or total; further knee replacements are total knee replacements. Patients transition through these states for their lifetime (up to age 100) or until they die (patients can move to death from any state). A detailed description of each health state included in the model is detailed below under “Health States” section.

Figure 16. Markov model structure



In this economic evaluation, combinations of primary and second repairs with the intervention and comparator treatments are considered. Patients will experience a secondary repair following failure of the primary repair. The possible combinations are:

- *Spherox followed by Spherox*
- *Spherox followed by MF*
- *MF followed by Spherox*
- *MF followed by MACI*
- *MF followed by ChondroCelect*
- *MF followed by MF*
- *MACI followed by MACI*
- *MACI followed by MF*
- *ChondroCelect followed by ChondroCelect*
- *ChondroCelect followed by MF*

Health states

- Primary repair: The primary repair could be MF, MACI, ChondroCelect or Spherox. After the primary repairs, patients can then either move to the 'successful primary repair' health state, 'second repair' health state or 'no further repair' state.

- No further repair: No further repairs mean that patients rely on analgesics for pain relief rather than have another attempt at repair, although the patients may receive knee replacement later.

- Successful primary repair: Successful primary repair can be permanent or temporary. For permanent successful repairs, the first repair works and patients stay in the 'successful primary repair' health state; for temporary successful primary repair, the repair fails after patients are symptom free for years. Patients can then decide to either receive a second repair or have no further repair.

- Second repair: If the primary repair is MF, second repair can be either MF, MACI, ChondroCelect or Spherox. If the primary repair is ACI (MACI, ChondroCelect, or Spherox), the second repair can be either the same type of ACI or MF. Patients undergo second repair can move to successful second repair or no further repair.

- Successful second repair: Successful second repair can also be permanent or temporary, with patients stay in the 'successful second repair' health state or move to 'no further repair' health state respectively.

- First knee replacement: At age 55, patients are eligible to receive first knee replacements, which can be partial or total. Patients can move this health state to the 'successful first knee replacement', 'further knee replacement' or 'no further knee replacement' health states.

- Successful first knee replacement: Successful first knee replacement can be permanent or temporary as knee replacement tends to fail over time, which

moves the patients to either ‘further knee replacement’ or ‘no further knee replacement’ health state.

- No further knee replacement: Patients who move to ‘no further knee replacement’ health state choose not to receive another knee replacement and stay in this health state until they die.

- Further knee replacement: All further knee replacements are TKRs per expert clinical opinion as reported by Mistry et al. Patients in this health state can move to ‘successful further knee replacement’ or ‘no further knee replacement’ health state. There is no limit in the model to the number of knee replacements patients can receive.

- Successful further knee replacement: If the successful further knee replacement is permanent, patients can stay in that state for the rest of their life; otherwise, they can either receive another knee replacement or choose to have no further knee replacement. There is no limit in the model to the number of knee replacements patients can receive.

- Death: it is an absorbing health state.

Cycle length

The cycle length is one year which allows patients to recover from surgery. Transitions between each health state occur at the end of each cycle.

Time horizon

A lifetime horizon (i.e. patients can live to 100 years) is adopted in the base case. This duration is sufficiently long to ensure that all potentially relevant costs and benefits experienced over the long-term were not omitted from the analysis.

Intervention technology and comparators

The intervention technology in this appraisal submission is Spherox, an autologous chondrocyte implantation (ACI) that uses a technique in which the patients' own cartilage cells (chondrocytes) are developed in vitro. Cultured chondrocytes are seeded into agarose to form stable chondrocyte aggregates (spheroids). These spheroids, or "microtissues", are induced to form cartilage-like tissue and transplanted into the defect.

The final scope issued by NICE stated that comparators may include MF, ACI, knee lavage/debridement, mosaicplasty, osteotomy, and best supportive care. Knee lavage/debridement, mosaicplasty, osteotomy, and best supportive care are not considered relevant comparators for this decision problem, therefore the comparator technologies included in this analysis are MF and other ACI technologies (MACI and ChondroCelect) [SeeB.1.1 Decision problem].

MF is a marrow-stimulating method, during which small holes are drilled through the surface of the bone in damaged cartilage areas. While stem cells are carried from the bone marrow to areas where the damaged cartilage has been debrided, scar cartilages called fibrocartilage could be formed. The main drawback of the technique is that instead of normal hyaline cartilage that is mainly composed of type II collagen, fibrocartilage is composed of type I collagen, which is less resilient and hardwearing (32).

Both MACI and ChondroCelect are 3rd generation of ACI with a two-step procedure, consisting of one arthroscopy for cartilage harvesting and one arthrotomy for implantation of cultured chondrocytes. With MACI, the chondrocytes are seeded on to a scaffold composed of type I/III collagen and implanted into defected area of the knee (23).

ChondroCelect uses the Characterised Chondrocyte Implantation technique, with which chondrocytes with the most potential to produce hyaline cartilage are identified by a panel of biomarkers. The characterised cells are then expanded ex vivo for implantation (43).

B.3.3 Clinical parameters and variables

3.3.1 Clinical inputs

The clinical inputs used in the model were derived using efficacy data from the Phase III TIG/ACT, SUMMIT and COWISI trials (see B.2 Clinical effectiveness) and relative risks derived from an NMA (see

B.2.9 Indirect and mixed treatment comparisons). The definition of responder varies across the included studies, this is extensively described in section B.2.9. The definition of treatment failure was the need for revision surgery. Primary outcomes from the individual trials included in the analyses are listed in **Error! Reference source not found.** (Appendix D). An indirect comparison was conducted to inform treatment effects for the comparators in this analyses. Detailed of the methodology and findings can be found in section B.2.9 (Figure 12 and Figure 13). Values listed in Table 47 below, represent the treatment effects used in the model during the trial period and to populate the transition probabilities used for the subsequent years.

3.3.2 Calculation of Transition probabilities

Trial and NMA data was cycle adjusted for implementation into the model as transition probabilities (i.e. the 2 year rates were converted to one-year probabilities) which are shown in transition matrices below which are categorised by age group (20-54 and 55+). Transition probabilities vary between age groups because patients become eligible to receive knee replacement at the age of 55.

Transition probabilities for success and failure for patients who received a knee replacement or knee replacement revision have been obtained from Mistry et al (32). It was assumed that transition probabilities for patients receiving a partial or total knee replacement were the same. These probabilities can be found in Table 50 below.

3.3.3 Transition probabilities over time

The data derived from trials and incorporating relative risks from the NMA apply to the lifetime of the model (as probabilities) except the failure rates for MACI and Spherox; these rates ([redacted] were used in the first two years of the model (the length of the trials) but did not seem reasonable to extrapolate to future years. A conservative estimate of

1.25% failure rate was used based on a similar assumption taken by Mistry et al (32). In Mistry et al, it was assumed that 12.5% of the non-responders will move to the no further repair health state and of these 12.5%, they assumed that 10% of them will move from the successful primary to the second repair health state (1.25%). This has been applied to the current analysis due to the lack of long term data. The same assumption has been applied to both Spherox and MACI, while fro MF and ChondroCelect, a proportion of patients report required a second surgery during the trial period. The same proportion of patients (adjusted by cycle length) has been assumed to be applicable for the all subsequent years in the economic model.

Table 47. Clinical inputs – rates used in the model

Intervention	Spherox (%)	MF (%)*	MACI (%)*	ChondroCelect (%)*
First two years (Trial period)				
No. of responders (%)	[redacted]	79.98%	86.88	86.57
No. non-responders (%)	[redacted]	20.02%	13.12	13.43
No. requiring second repair (%)	[redacted]	3.44%	0.00	1.01
Subsequent years (Cycle adjusted trial probabilities)				
No. of responders (%)	90.00	89.43	93.21	93.04
No. non-responders (%)	10.00	10.57	6.79	6.96
No. requiring second repair (%)	0.63	1.73	0.63	1.13

*data obtained by applying the RR from the NMA to the Spherox treatment effect

Table 48 Annual transition probabilities – 20 to 54 years

From\to	Successful primary	Second repair	Successful second	No further repair		Successful primary	Second repair	Successful second	No further repair
	Spherox followed by Spherox					**Spherox followed by MF**			
Primary repair	0.9000	0.0000	-	0.1000		0.9000	0.0000	-	0.1000
Successful primary	0.4437	0.0063	-	0.5500		0.4437	0.0063	-	0.5500
Second repair	-	-	0.9000	0.1000		-	-	0.8943	0.1057
Successful second	-	-	0.4359	0.5641		-	-	0.4475	0.5525
No further repair	-	-	-	1.0000		-	-	-	1.0000
	MACI followed by MACI					**MACI followed by MF**			
Primary repair	0.9321	0.0000	-	0.0679		0.9321	0.0000	-	0.0679
Successful primary	0.3728	0.0063	-	0.6209		0.3728	0.0063	-	0.6209
Second repair	-	-	0.9321	0.0679		-	-	0.8943	0.1057
Successful second	-	-	0.3622	0.6378		-	-	0.4475	0.5525
No further repair	-	-	0.0000	1.0000		-	-	-	1.0000
	ChondroCelect followed by ChondroCelect					**ChondroCelect followed by MF**			
Primary repair	0.9308	0.0051	-	0.0641		0.9308	0.0051	-	0.0641
Successful primary	0.3768	0.0063	-	0.6169		0.3768	0.0063	-	0.6169
Second repair	-	-	0.9304	0.0696		-	-	0.8943	0.1057
Successful second	-	-	0.3664	0.6336		-	-	0.4475	0.5525
No further repair	-	-	0.0000	1.0000		-	-	-	1.0000
	MF followed by MF					**MF followed by Spherox**			
Primary repair	0.8952	0.0086	-	0.0961		0.8914	0.0086	-	0.1000
Successful primary	0.4577	0.0086	-	0.5337		0.4577	0.0086	-	0.5337
Second repair	-	-	0.8943	0.1057		-	-	0.9000	0.1000
Successful second	-	-	0.4475	0.5525		-	-	0.4359	0.5641
No further repair	-	-	0.0000	1.0000		-	-	0.0000	1.0000
	MF followed by MACI					**MF followed by ChondroCelect**			
Primary repair	0.8952	0.0086	-	0.0961		0.8952	0.0086	-	0.0961
Successful primary	0.4577	0.0086	-	0.5337		0.4577	0.0086	-	0.5337
Second repair	-	-	0.9321	0.0679		-	-	0.9304	0.0696
Successful second	-	-	0.3622	0.6378		-	-	0.3664	0.6336
No further repair	-	-	0.0000	1.0000		-	-	0.0000	1.0000

Table 49: Annual transition probabilities - 55 years+

From\to	Successful primary	Second repair	Successful second	No further repair	First TKR	First PKR		Successful primary	Second repair	Successful second	No further repair	First TKR	First PKR
	Spherox followed by Spherox							**Spherox followed by MF**					
Successful primary	0.4336	0.0063	0.0000	0.5500	0.0051	0.0051		0.4336	0.0063	0.0000	0.5500	0.0051	0.0051
Second repair	0.0000	0.0000	0.9000	0.1000	0.0000	0.0000		0.0000	0.0000	0.8943	0.1057	0.0000	0.0000
Successful second	0.0000	0.0000	0.4258	0.5641	0.0051	0.0051		0.0000	0.0000	0.4374	0.5525	0.0051	0.0051
No further repair	0.0000	0.0000	0.0000	0.9899	0.0051	0.0051		0.0000	0.0000	0.0000	0.9899	0.0051	0.0051
	MACI followed by MACI							**MACI followed by MF**					
Successful primary	0.3627	0.0063	0.0000	0.6209	0.0051	0.0051		0.3627	0.0063	0.0000	0.6209	0.0051	0.0051
Second repair	0.0000	0.0000	0.9321	0.0679	0.0000	0.0000		0.0000	0.0000	0.8943	0.1057	0.0000	0.0000
Successful second	0.0000	0.0000	0.3521	0.6378	0.0051	0.0051		0.0000	0.0000	0.4374	0.5525	0.0051	0.0051
No further repair	0.0000	0.0000	0.0000	0.9899	0.0051	0.0051		0.0000	0.0000	0.0000	0.9899	0.0051	0.0051
	ChondroCelect followed by ChondroCelect							**ChondroCelect followed by MF**					
Successful primary	0.3667	0.0063	0.0000	0.6169	0.0051	0.0051		0.3667	0.0063	0.0000	0.6169	0.0051	0.0051
Second repair	0.0000	0.0000	0.9304	0.0696	0.0000	0.0000		0.0000	0.0000	0.8943	0.1057	0.0000	0.0000
Successful second	0.0000	0.0000	0.3563	0.6336	0.0051	0.0051		0.0000	0.0000	0.4374	0.5525	0.0051	0.0051
No further repair	0.0000	0.0000	0.0000	0.9899	0.0051	0.0051		0.0000	0.0000	0.0000	0.9899	0.0051	0.0051
	MF followed by MF							**MF followed by Spherox**					
Successful primary	0.4476	0.0086	0.0000	0.5337	0.0051	0.0051		0.4476	0.0086	0.0000	0.5337	0.0051	0.0051
Second repair	0.0000	0.0000	0.8943	0.1057	0.0000	0.0000		0.0000	0.0000	0.9000	0.1000	0.0000	0.0000
Successful second	0.0000	0.0000	0.4374	0.5525	0.0051	0.0051		0.0000	0.0000	0.4258	0.5641	0.0051	0.0051
No further repair	0.0000	0.0000	0.0000	0.9899	0.0051	0.0051		0.0000	0.0000	0.0000	0.9899	0.0051	0.0051
	MF followed by MACI							**MF followed by ChondroCelect**					
Successful primary	0.4476	0.0086	0.0000	0.5337	0.0051	0.0051		0.4476	0.0086	0.0000	0.5337	0.0051	0.0051
Second repair	0.0000	0.0000	0.9321	0.0679	0.0000	0.0000		0.0000	0.0000	0.9304	0.0696	0.0000	0.0000
Successful second	0.0000	0.0000	0.3521	0.6378	0.0051	0.0051		0.0000	0.0000	0.3563	0.6336	0.0051	0.0051
No further repair	0.0000	0.0000	0.0000	0.9899	0.0051	0.0051		0.0000	0.0000	0.0000	0.9899	0.0051	0.0051

Table 50 Annual transition probabilities - 55 years + (for all scenarios)

From\to	Successful first TKR	Successful first PKR	Further KR	Successful further KR	No further KR
	All comparisons				
First TKR	0.9922	0.0000	0.0058	0.0000	0.0020
First PKR	0.0000	0.9922	0.0058	0.0000	0.0020
Successful first TKR	0.9731	0.0000	0.0108	0.0000	0.0162
Successful first PKR	0.0000	0.9731	0.0108	0.0000	0.0162
Further KR	0.0000	0.0000	0.0000	0.9792	0.0209
Successful further KR	0.0000	0.0000	0.0108	0.9731	0.0162
No further KR	0.0000	0.0000	0.0000	0.0000	1.0000

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

In the Phase II and Phase III trials for Spherox, patient primary outcomes were assessed using the knee injury and osteoarthritis outcomes scale (KOOS). Patient reported HRQOL using instruments preferred by NICE in the reference case, e.g. EQ-5D, were not available from the trials. The values from Mistry et al (32), which informed the most recent NICE appraisal in this therapy area, were the most applicable as they were used to address a similar decision problem. Specifically:

- The economic model developed for this submission followed the same structure
- The population and indication for this submission are the same
- All technologies assessed in Mistry et al except for traditional ACI are included in this submission

The utility values for each health state are described in detail in the “Health-related quality of life data used in used in the cost-effectiveness analysis” section.

Mapping

No mapping was performed.

Health-related quality-of-life studies

A systematic literature search was conducted to locate utility values that were suitable for inclusion in the economic model and the outcomes of the search are summarised

in Appendix H. 12 HRQoL studies were identified in the search. In addition to Clar et al (28), Derrett et al (29), Elvidge et al (30), Gerlier et al (31), Mistry et al (32) and Samuelson and Brown (33), six more studies [Batty and Birrell (44), Dong and Buxton (39), Health and Social Care Information Centre (45), Janssen and Granath (38), Kind et al (46), Ruchlin and Insinga (47)] reporting utility values associated with knee replacement procedures and age-related utility decline were further extracted from Elvidge et al and Mistry et al.

For knee repairs, Clar et al could not identify reliable utility data to calculate QALY because the required data were not available. Samuelson and Brown adapted the utility data for OA patients (48) to patients with a focal chondral defect because no specific utility values were identified. Preference-based utility values were reported by Derrett et al, Elvidge et al, Gerlier et al and Mistry et al, which are suitable for the economic evaluation. Derrett et al collected EQ-5D data two years post intervention. Gerlier et al mapped EQ-5D from SF-36 data collected during the five-year follow-up of the TIG/ACT trial (4). Although Elvidge et al derived the utility data from the same trial, the duration of follow-up used was not reported. The TIG/ACT trial is the main source of utility values therefore the utility values used in Mistry et al were derived from Gerlier et al. Knee replacement related utility values were derived from Elvidge et al, Batty and Birrell (44), Health and Social Care Information Centre (45) and Ruchlin and Insinga (47). In Mistry et al, utility values of pre-KR, successful KR, before further KR, successful further KR and no further repair were derived from the data in Dong and Buxton (39), Gerlier et al and Jansson and Granath (38). Age-related utility decline reported by Kind et al (46) were considered by both Elvidge et al and Mistry et al. For the cost effectiveness analysis of Spherox, the preferred utility values are those from Mistry et al supplemented by Dong and Buxton, Janssen and Granath.

Adverse reactions

Adverse reactions were not considered in this analysis and as such no amendments to HRQOL were made based on this. This is aligned with the methods used by Mistry et al.

Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values were derived directly from the analysis as reported by Mistry et al (32) which used a combination of values from Gerlier et al (31) (utilities related to the first intervention), Dong and Buxton (39), and Janssen and Granath (38) (utility values for knee replacement). Per methods used by Mistry et al the ACIs, (including Spherox) are treated as a class in terms of HRQOL benefits, and therefore all share the same utility values for health states. As such, in the following description, the term ACI will be used to cover all types of ACIs in the model (MACI, ChondroCelect, and Spherox).

First repair

Patients with symptomatic articular cartilage defects in the knee experience pain and difficulty in moving, which is reflected in the baseline utility value before primary repair. In the first year of successful primary or second surgery, patients have an improvement in utility but is limited by the experience of having outpatient visits, the operation, and rehabilitation visits over the first year. Following the first year, patients with successful repairs are assumed to have made improvements in recovery and experience an even higher utility. For patients receiving ACI, this higher utility is maintained for as long as patients stay in that state. In contrast, for patients receiving MF, which is not expected to provide a permanent repair, the utility score is maintained until the fifth year following repair, at which point it falls to the pre-repair level. For patients that choose not to have further repair after an unsuccessful primary, it's assumed they retain some benefit from surgery, which is reflected in the slightly higher utility value from pre-repair utility.

Second repair

Before second repair, patients return to a lower utility level equal to the baseline utility before primary repair, assuming their knee function and therefore quality of life deteriorates. After a second repair, patients either have no further repairs, during which they have the same utility as those that choose not to have a second repair following primary, or they have a successful repair. The utilities following successful second repair are conditional on the primary repair received (MF or an ACI). For patients that received ACI, the utilities for secondary repair are the same following primary repair. For patients that received MF, the utilities for secondary repair with ACI

begin to decrease after the fourth year and beyond because ACI is not expected to have as much benefit after MF. The utilities for patients receiving MF (following MF) are the same as primary repair.

Knee replacement

The following description of utility values for knee replacements are not conditional upon the type of previous repair.

It is expected that patients in need of knee replacement would experience more severe symptoms than patients in need of repair, and would not be eligible for knee replacement until they turn 55. This results in an even lower quality of life than patients in need of a repair, which is reflected in the lower utility value for before first knee replacement (partial or total). Following successful replacement, patients experience an increase in HRQOL, and this value is the same whether it was first or further replacement. For those who fail and require further total knee replacements, the utility always drops to the lowest value reflecting the impact of previous surgery but also low quality of life associated with their reduced knee function. Similar for repairs, patients who choose not to have a further repair obtain higher utility values than those who require further intervention because they may still have some benefit and they are not undergoing invasive surgery.

Utility values for each health state used in the model are provided in Table 51.

Table 51. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval*
Before primary repair	0.654	0.589 to 0.719
Successful primary repair (ACI), yr 1	0.760	0.684 to 0.836
Successful primary repair (ACI), yr 2	0.817	0.735 to 0.899
Successful primary repair (ACI), yr 3	0.817	0.735 to 0.899
Successful primary repair (ACI), yr 4	0.817	0.735 to 0.899
Successful primary repair (ACI), yr 5+	0.817	0.735 to 0.899
Successful primary repair (MF), yr 1	0.760	0.684 to 0.836
Successful primary repair (MF), yr 2	0.817	0.735 to 0.899
Successful primary repair (MF), yr 3	0.817	0.735 to 0.899
Successful primary repair (MF), yr 4	0.817	0.735 to 0.899
Successful primary repair (MF), yr 5+	0.654	0.589 to 0.719

No further repair	0.691	0.622 to 0.760
Successful ACI(ACI), yr 1	0.760	0.684 to 0.836
Successful ACI(ACI), yr 2	0.817	0.735 to 0.899
Successful ACI(ACI), yr 3	0.817	0.735 to 0.899
Successful ACI(ACI), yr 4	0.817	0.735 to 0.899
Successful ACI(ACI), yr 5+	0.817	0.735 to 0.899
Successful ACI(MF), yr 1	0.760	0.684 to 0.836
Successful ACI(MF), yr 2	0.817	0.735 to 0.899
Successful ACI(MF), yr 3	0.817	0.735 to 0.899
Successful ACI(MF), yr 4	0.817	0.735 to 0.899
Successful ACI(MF), yr 5+	0.654	0.589 to 0.719
Successful MF(ACI), yr 1	0.760	0.684 to 0.836
Successful MF(ACI), yr 2	0.817	0.735 to 0.899
Successful MF(ACI), yr 3	0.817	0.735 to 0.899
Successful MF(ACI), yr 4	0.789	0.710 to 0.868
Successful MF(ACI), yr 5+	0.789	0.710 to 0.868
Successful MF(MF), yr 1	0.760	0.684 to 0.836
Successful MF(MF), yr 2	0.817	0.735 to 0.899
Successful MF(MF), yr 3	0.817	0.735 to 0.899
Successful MF(MF), yr 4	0.817	0.735 to 0.899
Successful MF(MF), yr 5+	0.654	0.589 to 0.719
First knee replacement	0.615	0.553 to 0.676
Successful first knee replacement	0.780	0.702 to 0.858
Further TKR	0.557	0.501 to 0.613
Successful further TKR	0.780	0.702 to 0.858
No further TKR	0.691	0.622 to 0.760

*Calculated assuming a standard error of 30%

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix I outlines the systematic literature review to search for studies reporting relevant cost and healthcare resource data. Four studies located in the literature search were from the UK perspective [Clar et al (28), Derrett et al (29), Elvidge et al (30), Mistry et al (32)]. Mistry et al provided the most relevant and recent information for this analysis. Four studies [Miller et al (26), Gerlier et al (31), Samuelson and Brown (33), and Zhang et al (27)] were from the perspective of other health systems and therefore not considered relevant.

Intervention and comparators' costs and resource use

For ACIs (Spherox, ChondroCelect, MACI), one procedure is performed to obtain cells for cultivation from the patient and one for transplanting the tissues back into the patient's knee. For ChondroCelect and MACI, this is costed as an arthroscopy plus an arthrotomy in line with methods from Mistry et al (32). For Spherox, this is costed as two arthroscopies in line with the SmPC (1). In addition, ACIs have a cost for cells that covers product kits, cell culture, staff, and transport services. MF involves one patient surgical procedure and therefore is costed as such, inclusive of the cost of the inpatient stay, in line with methods from Mistry et al. Values were taken from Mistry et al, which were originally derived from Clar et al (28), and inflated to 2015/16 prices (the latest inflation year from HCHS P&P index) (40).

Resource use for each procedure includes outpatient visits and rehabilitation visits. Unit costs for these were derived from NHS reference costs and shown in Table 52. The number of visits per procedure is shown in Table 53 and was taken from Mistry et al. Resource use for Spherox was assumed to be equal to the other ACIs.

Table 52. Unit costs for procedures

Item	Unit Cost (£)	Source
Arthroscopy (day case)	733.97	Mistry et al (32) (Table 22). Inflated to 2015/16 costs using HCHS pay and prices index (40)
Arthrotomy (day case)	1,064.78	Mistry et al (32) (Table 22). Inflated to 2015/16 costs using HCHS pay and prices index
Spherox cells	10,000.00	co.don - NHS list price
ChondroCelect cells	16,000.00	UK price of ACI; Mistry et al (32) (Table 22)
MACI cells	16,000.00	UK price of ACI Mistry et al (32) (Table 22)
MF	3,121.96	Inpatient procedure – includes cost of inpatient stay; Mistry et al (32) (Table 22). Inflated to 2015/16 costs using HCHS pay and prices index
Outpatient visit	120.63	NHS reference costs 2015/2016 (42); HRG code WF01A (non-admitted face-to-face consultant led outpatient attendance)
Rehabilitation visit	344.64	NHS reference costs 2015/2016 (42); HRG code REHABL2 (rehabilitation for joint replacement)

Table 53. Resource use for intervention and comparators

Technology	Outpatient visits	Rehabilitation visits	Source
Microfracture	3	3	Table 23, Mistry et al (32)
Spherox	6	3	
ChondroCelect	6	3	
MACI	6	3	

Health-state unit costs and resource use

The only health states where costs are applied are those when the patient undergoes a procedure. During this time, the patient accrues costs for the procedure and any resource use over that year (i.e. one cycle). These are therefore equal to the total cost per procedure experienced for one year. There are no difference in costs between primary and secondary repairs. Costs for the intervention, comparators, and knee replacements are shown below (Table 54). Unit costs and resource contributing to the knee replacements are provided in the section on "Miscellaneous unit costs and resource use".

Table 54. Health state unit costs

Health state (procedure)	Total cost (£)
MF	4,517.78
Spherox	13,225.65
ChondroCelect	19,556.45
MACI	19,556.45
First knee replacement (PKR or TKR)	5,807.26
TKR following PKR	5,807.26
TKR following TKR	13,637.79

Adverse reaction unit costs and resource use

Adverse events and complications were not considered in this analysis as they were assumed to have little impact on outcomes. This assumption is also taken by Mistry et al (32).

Miscellaneous unit costs and resource use

Other costs and resource use included in the model are related to knee replacements, which patients are eligible to receive after age 55. The cost for a total knee replacement following total knee replacement is higher than following partial due to the complicated nature of the procedure and therefore requires an inpatient stay of 4.5

days. This follows the methods described by Mistry et al (32). In addition to the cost of procedures, for which unit costs are shown below (Table 55), all knee replacements include the cost of two outpatient visits in the year following the procedure (Table 56). This also follows the methods by Mistry et al which used clinical experts to derive the resource use used in the economic model.

Table 55. Unit costs for knee replacements

Item	Unit Cost (£)	Source
First knee replacement (partial or total)	£5,566.00	National Prices and National Tariff 2016/17 (41)
TKR following PKR	£5,566.00	National Prices and National Tariff 2016/17
TKR following TKR	£13,396.53*	Mistry et al (32) (Table 22). Inflated to 2015/16 costs using HCHS pay and prices index

*The cost of inpatient stay is included

Table 56. Resource use for knee replacements

Technology	Outpatient visits	Rehabilitation visits	Source
Knee replacement (any)	2	0	Mistry et al (32) (Table 23)

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 57. Base-case inputs

Variable	Value	Distribution	Measurement of uncertainty: CI	Reference to section in submission
Patients				
Age	33	Beta	26.4 to 39.6	See B.2.7.1 Phase III trial page
% male	0.6	Beta	0.48 to 0.72	See B.2.3.1 Phase III trial, Baseline characteristics of the study population page
Cost				
MACI	19556.45	Beta	15645.16 to 23467.74	See B3.5, Health-state unit costs and resource use page, Table
MF	4517.78	Beta	3614.22 to 5421.33	
ChondroCelect	19556.45	Beta	15645.16 to 23467.74	
Spherox	13225.65	Beta	10580.52 to 15870.78	
1st TKR	5807.26	Beta	4645.81 to 6968.71	
TKR following PKR	5807.26	Beta	4645.81 to 6968.71	

TKR following TKR	13637.79	Beta	10910.23 to 16365.35	
Parameters for ages 20-54				
Clinical; Spherox -> MF				
MF repair | Primary Spherox	0.00	Beta	0	See B.3.3.3 Transition probabilities over time page
No further repair | Primary Spherox	0.10	Beta	0.08 to 0.12	
MF repair | Successful Spherox	0.01	Beta	0.005 to 0.008	
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
Clinical; Spherox -> Spherox				
Spherox repair | Primary Spherox	0.00	Beta	0	See B.3.3.3 Transition probabilities over time page
No further repair | Primary Spherox	0.10	Beta	0.08 to 0.12	
Spherox repair | Successful Spherox	0.01	Beta	0.005 to 0.008	
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66	
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12	
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68	
Clinical; MACI -> MF				
MF repair | Primary MACI	0.00	Beta	0	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MACI	0.07	Beta	0.05 to 0.08	
MF repair | Successful MACI	0.01	Beta	0.005 to 0.008	
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
Clinical; MACI -> MACI				
MACI repair | Primary MACI	0.00	Beta	0	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MACI	0.07	Beta	0.05 to 0.08	
MACI repair | Successful MACI	0.01	Beta	0.005 to 0.008	

No further repair | Successful MACI	0.62	Beta	0.50 to 0.75	
No further repair | MACI repair	0.07	Beta	0.05 to 0.08	
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77	
Clinical; ChondroCelect -> MF				
MF repair | Primary ChondroCelect	0.01	Beta	0.00 to 0.01	See B.3.3.3 Transition probabilities over time page
No further repair | Primary ChondroCelect	0.06	Beta	0.05 to 0.08	
MF repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008	
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
Clinical; ChondroCelect -> ChondroCelect				
ChondroCelect repair | Primary ChondroCelect	0.01	Beta	0.00 to 0.01	See B.3.3.3 Transition probabilities over time page
No further repair | Primary ChondroCelect	0.06	Beta	0.05 to 0.08	
ChondroCelect repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008	
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74	
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08	
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76	
Clinical; MF -> Spherox				
Spherox repair | Primary MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MF	0.10	Beta	0.08 to 0.12	
Spherox repair | Successful MF	0.01	Beta	0.007 to 0.010	
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12	

No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68	
Clinical; MF -> MACI				
MACI repair | Primary MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MF	0.10	Beta	0.08 to 0.12	
MACI repair | Successful MF	0.01	Beta	0.007 to 0.010	
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
No further repair | MACI repair	0.07	Beta	0.05 to 0.08	
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77	
Clinical; MF -> ChondroCelect				
ChondroCelect repair | Primary MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MF	0.10	Beta	0.08 to 0.12	
ChondroCelect repair | Successful MF	0.01	Beta	0.007 to 0.010	
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08	
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76	
Clinical; MF -> MF				
MF repair | Primary MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Primary MF	0.10	Beta	0.08 to 0.12	
MF repair | Successful MF	0.01	Beta	0.007 to 0.010	
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
Parameters for ages 55+				
Clinical; Spherox -> MF				
MF repair | Successful Spherox	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66	

First TKR/PKR | Successful Spherox	0.01	Beta	0.00 to 0.01	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; Spherox -> Spherox				
Spherox repair | Successful Spherox	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66	
First TKR/PKR | Successful Spherox	0.01	Beta	0.00 to 0.01	
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12	
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68	
First TKR/PKR | Successful Spherox repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MACI -> MF				
MF repair | Successful MACI	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75	
First TKR/PKR | Successful MACI	0.01	Beta	0.00 to 0.01	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MACI -> MACI				
MACI repair | Successful MACI	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75	
First TKR/PKR | Successful MACI	0.01	Beta	0.00 to 0.01	

No further repair | MACI repair	0.07	Beta	0.05 to 0.08	
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77	
First TKR/PKR | Successful MACI repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; ChondroCelect -> MF				
MF repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74	
First TKR/PKR | Successful ChondroCelect	0.01	Beta	0.00 to 0.01	
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; ChondroCelect -> ChondroCelect				
ChondroCelect repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008	See B.3.3.3 Transition probabilities over time page
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74	
First TKR/PKR | Successful ChondroCelect	0.01	Beta	0.00 to 0.01	
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08	
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76	
First TKR/PKR | Successful ChondroCelect repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MF -> Spherox				
Spherox repair | Successful MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition

No further repair | Successful MF	0.53	Beta	0.43 to 0.64	probabilities over time page
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01	
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12	
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68	
First TKR/PKR | Successful Spherox repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MF -> MACI				
MACI repair | Successful MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01	
No further repair | MACI repair	0.07	Beta	0.05 to 0.08	
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77	
First TKR/PKR | Successful MACI repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MF -> ChondroCelect				
ChondroCelect repair | Successful MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition probabilities over time page
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01	
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08	
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76	
First TKR/PKR | Successful ChondroCelect repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical; MF -> MF				
MF repair | Successful MF	0.01	Beta	0.007 to 0.010	See B.3.3.3 Transition
No further repair | Successful MF	0.53	Beta	0.43 to 0.64	

First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01	probabilities over time page
No further repair | MF repair	0.11	Beta	0.08 to 0.13	
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66	
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01	
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01	
Clinical: TKR				
Further KR | First TKR/PKR	0.01	Beta	0.00 to 0.01	See B.3.3.3 Transition probabilities over time page
No further KR | First TKR/PKR	0.00	Beta	0	
Further KR | Successful first TKR/PKR	0.01	Beta	0.009 to 0.013	
No further KR | Successful first TKR/PKR	0.02	Beta	0.01 to 0.02	
No further KR | Further KR	0.02	Beta	0.02 to 0.03	
Further KR | Successful further KR	0.01	Beta	0.009 to 0.013	
No further KR | Successful further KR	0.02	Beta	0.01 to 0.02	
Ratio of TKR:PKR	0.50	Beta	0.40 to 0.60	
Procedure mortality, TKR1	0.01	Beta	0.006 to 0.008	
Procedure mortality, TKR2	0.01	Beta	0.009 to 0.013	
HRQoL				
HRQoL before primary repair	0.65	Beta	0.52 to 0.78	See B.3.3.3 Transition probabilities over time page B3.4, Health-related quality-of-life data used in the cost-effectiveness analysis page, Table
HRQoL, Primary ACI (Spherox, MACI, ChondroCelect), yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, Primary ACI (Spherox, MACI, ChondroCelect), yr 2+	0.82	Beta	0.65 to 0.98	
HRQoL, Primary MF, yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, Primary MF, yr 2-4	0.82	Beta	0.65 to 0.98	
HRQoL, Primary MF, yr5	0.65	Beta	0.52 to 0.78	
HRQoL, Before 2nd repair	0.65	Beta	0.52 to 0.78	

HRQoL, No 2nd repair	0.69	Beta	0.55 to 0.83	
HRQoL, ACI | 1st ACI, yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, ACI | 1st ACI, yr 2+	0.82	Beta	0.65 to 0.98	
HRQoL, MF | 1st ACI, yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, MF | 1st ACI, yr 2-4	0.82	Beta	0.65 to 0.98	
HRQoL, MF | 1st ACI, yr 5	0.65	Beta	0.52 to 0.78	
HRQoL, ACI | 1st MF, yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, ACI | 1st MF, yr 2-3	0.82	Beta	0.65 to 0.98	
HRQoL, ACI | 1st MF, yr 4-5	0.79	Beta	0.63 to 0.95	
HRQoL, MF | 1st MF, yr 1	0.76	Beta	0.61 to 0.91	
HRQoL, MF | 1st MF, yr 2-4	0.82	Beta	0.65 to 0.98	
HRQoL, MF | 1st MF, yr 5	0.65	Beta	0.52 to 0.78	
HRQoL, No further repair	0.69	Beta	0.55 to 0.83	
HRQoL, Before 1st KR	0.62	Beta	0.49 to 0.74	
HRQoL, Successful 1st KR | TKR/PKR	0.78	Beta	0.62 to 0.94	
HRQoL, Before 2nd KR	0.56	Beta	0.45 to 0.67	
HRQoL, Successful 2nd KR	0.78	Beta	0.62 to 0.94	
HRQoL, No further KR	0.69	Beta	0.55 to 0.83	

Assumptions

The key structural and input assumptions incorporated in the model are detailed with justification and associated sensitivity analyses (if any) in Table 58.

Table 58: Key structural and input assumptions

	Assumption	Justification	Sensitivity Analysis
1	A lifetime horizon is appropriate for the base-case analysis	Shorter time horizons may not capture the full cost and/or benefits relevant to the decision problem. This time horizon is also modelled as the base case in other published analyses in the same disease area.	Varying time horizons are tested in the scenario analysis

2	The efficacy of technologies derived from trials and NMA is generalisable to the proposed patient population in England and Wales	Lack of data	Values tested in the OWSA and PSA
3	The efficacy of technologies, except for some failure rate data (see Assumption 4), derived from trials and NMA is applicable for the patients' lifetime and is extrapolated over the entire time model horizon	Lack of data	Values tested in the OWSA and PSA
4	The failure rate for MACI and Spherox from trials does not continue after year 2	Failure rates from the 2 year trial data from MACI and Spherox are 0%. It did not seem reasonable to extrapolate beyond the first 2 years of the model. In future years a 1.25% failure rate was used. This assumption is also taken by Mistry et al (32).	Values tested in the OWSA and PSA
5	The efficacy of the technologies' after primary repair are equal to efficacy after secondary repair	Data is not available on the efficacy following secondary repair. This assumption is also taken by Mistry et al (32).	Values tested in the OWSA and PSA
6	50%/50% PKR/TKR for first repair	This assumption is also taken by Mistry et al (32).	Varying proportions of PKR/TKR are tested in the scenario analysis
7	Utilities from Mistry et al (32) are applicable to this model	This provides consistency and comparability of technologies for the same indication	Values tested in the OWSA and PSA
8	The utilities for Spherox are equal to other ACIs in the model	Data on patient HRQoL from Spherox trials is not available. This conservative assumption provides consistency and comparability of technologies.	Values tested in the OWSA and PSA
9	Adverse events or complications are not considered	Adverse events or complications are assumed to have little impact on the outcomes of the analyses. This assumption is also taken by Mistry et al (32).	Not tested

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Results of the base-case incremental cost-effectiveness analysis for the average patient are shown in the tables below. Table 59 shows results for Spherox versus comparators that are currently available in the UK market, i.e. MF. **Error! Reference source not found.** shows results for Spherox versus all the comparators listed in the decision problem. Treatment combinations (primary followed by secondary repair) are

listed from least to most expensive, then ranked in terms of dominance and extended dominance.

See appendix J for clinical outcomes from the model and disaggregated results.

Table 59. Base case results - Spherox vs. currently available technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	£5,763	23.039	15.8510	..	..	..	..
MF -> Spherox	£7,156	23.039	15.8514				Ext. Dominated
Spherox -> MF	£14,182	23.039	17.9711		0.000		3,971
Spherox -> Spherox	£15,017	23.039	17.9717		0.000		1,391,667
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 60: Base case results – Spherox vs. all technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	£5,763	23.039	15.8510	..	..	..	..
MF -> Spherox	£7,156	23.039	15.8514				Ext. Dominated
MF -> ChondroCelect	£8,168	23.039	15.8492				Dominated
MF -> MACI	£8,168	23.039	15.8490				Dominated
Spherox -> MF	£14,182	23.039	17.9711	£8,419	0.000	2.1201	£3,971
Spherox -> Spherox	£15,017	23.039	17.9717				Ext. Dominated
MACI -> MF	£20,544	23.039	18.1168	£6,362	0.000	0.1457	£43,676
ChondroCelect -> MF	£20,588	23.039	18.1101				Dominated
MACI -> MACI	£22,091	23.039	18.1157				Dominated
ChondroCelect -> ChondroCelect	£22,283	23.039	18.1090				Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) was based on a willingness to pay threshold of £20,000 per QALY. The PSA was conducted using 1,000 simulations. Because several comparator technologies are included in this analysis, a PSA scatterplot on the cost-effectiveness plane was not generated. A cost-effectiveness acceptability frontier (CEAF) is presented below.

PSA was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning specific parametric distributions and repeatedly sampling mean parameter values. Sampling was based on point estimates used in the deterministic analysis and where standard errors were not avaliable, a default of 20% of the mean (point estimate) was used.

Each group of samples from all of the parameters included in the PSA generated an estimate for total costs and effects. A total of 1,000 different samples were taken from all distributions so that all values of a parameter are likely to have been present in the range of outputs.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported in Table 61.

Table 62. Variables included in the PSA

Input	Mean	Distribution type	CI of distribution
Patients			
% male	0.60	Beta	0.48 to 0.72
Cost			
MF	4,518	Gamma	3,614 to 5,421
1st TKR	5,807	Gamma	4,646 to 6,969
TKR following PKR	5,807	Gamma	4,646 to 6,969
Spherox	13,226	Gamma	10,581 to 15,870
TKR following TKR	13,638	Gamma	10,910 to 16,365
MACI	19,556	Gamma	15,645 to 23,468
ChondroCelect	19,556	Gamma	15,645 to 23,467
Parameters for ages 20-54			
Clinical; Spherox -> MF			
MF repair | Primary Spherox	0.00	Beta	0
No further repair | Primary Spherox	0.10	Beta	0.08 to 0.12

MF repair | Successful Spherox	0.01	Beta	0.005 to 0.008
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
Clinical; Spherox -> Spherox			
Spherox repair | Primary Spherox	0.00	Beta	0
No further repair | Primary Spherox	0.10	Beta	0.08 to 0.12
Spherox repair | Successful Spherox	0.01	Beta	0.005 to 0.008
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68
Clinical; MACI -> MF			
MF repair | Primary MACI	0.00	Beta	0
No further repair | Primary MACI	0.07	Beta	0.05 to 0.08
MF repair | Successful MACI	0.01	Beta	0.005 to 0.008
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
Clinical; MACI -> MACI			
MACI repair | Primary MACI	0.00	Beta	0
No further repair | Primary MACI	0.07	Beta	0.05 to 0.08
MACI repair | Successful MACI	0.01	Beta	0.005 to 0.008
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75
No further repair | MACI repair	0.07	Beta	0.05 to 0.08
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77
Clinical; ChondroCelect -> MF			
MF repair | Primary ChondroCelect	0.01	Beta	0.00 to 0.01
No further repair | Primary ChondroCelect	0.06	Beta	0.05 to 0.08
MF repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
Clinical; ChondroCelect -> ChondroCelect			
ChondroCelect repair | Primary ChondroCelect	0.01	Beta	0.00 to 0.01
No further repair | Primary ChondroCelect	0.06	Beta	0.05 to 0.08
ChondroCelect repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76
Clinical; MF -> Spherox			
Spherox repair | Primary MF	0.01	Beta	0.007 to 0.010
No further repair | Primary MF	0.10	Beta	0.08 to 0.12
Spherox repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12

No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68
Clinical; MF -> MACI			
MACI repair | Primary MF	0.01	Beta	0.007 to 0.010
No further repair | Primary MF	0.10	Beta	0.08 to 0.12
MACI repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
No further repair | MACI repair	0.07	Beta	0.05 to 0.08
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77
Clinical; MF -> ChondroCelect			
ChondroCelect repair | Primary MF	0.01	Beta	0.007 to 0.010
No further repair | Primary MF	0.10	Beta	0.08 to 0.12
ChondroCelect repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76
Clinical; MF -> MF			
MF repair | Primary MF	0.01	Beta	0.007 to 0.010
No further repair | Primary MF	0.10	Beta	0.08 to 0.12
MF repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
Parameters for ages 55+			
Clinical; Spherox -> MF			
MF repair | Successful Spherox	0.01	Beta	0.005 to 0.008
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful Spherox	0.01	Beta	0.00 to 0.01
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; Spherox -> Spherox			
Spherox repair | Successful Spherox	0.01	Beta	0.005 to 0.008
No further repair | Successful Spherox	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful Spherox	0.01	Beta	0.00 to 0.01
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68
First TKR/PKR | Successful Spherox repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MACI -> MF			
MF repair | Successful MACI	0.01	Beta	0.005 to 0.008
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75
First TKR/PKR | Successful MACI	0.01	Beta	0.00 to 0.01
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01

First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MACI -> MACI			
MACI repair | Successful MACI	0.01	Beta	0.005 to 0.008
No further repair | Successful MACI	0.62	Beta	0.50 to 0.75
First TKR/PKR | Successful MACI	0.01	Beta	0.00 to 0.01
No further repair | MACI repair	0.07	Beta	0.05 to 0.08
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77
First TKR/PKR | Successful MACI repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; ChondroCelect -> MF			
MF repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74
First TKR/PKR | Successful ChondroCelect	0.01	Beta	0.00 to 0.01
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; ChondroCelect -> ChondroCelect			
ChondroCelect repair | Successful ChondroCelect	0.01	Beta	0.005 to 0.008
No further repair | Successful ChondroCelect	0.62	Beta	0.49 to 0.74
First TKR/PKR | Successful ChondroCelect	0.01	Beta	0.00 to 0.01
No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76
First TKR/PKR | Successful ChondroCelect repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MF -> Spherox			
Spherox repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01
No further repair | Spherox repair	0.10	Beta	0.08 to 0.12
No further repair | Successful Spherox repair	0.56	Beta	0.45 to 0.68
First TKR/PKR | Successful Spherox repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MF -> MACI			
MACI repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01
No further repair | MACI repair	0.07	Beta	0.05 to 0.08
No further repair | Successful MACI repair	0.64	Beta	0.51 to 0.77
First TKR/PKR | Successful MACI repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MF -> ChondroCelect			
ChondroCelect repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01

No further repair | ChondroCelect repair	0.07	Beta	0.06 to 0.08
No further repair | Successful ChondroCelect repair	0.63	Beta	0.51 to 0.76
First TKR/PKR | Successful ChondroCelect repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical; MF -> MF			
MF repair | Successful MF	0.01	Beta	0.007 to 0.010
No further repair | Successful MF	0.53	Beta	0.43 to 0.64
First TKR/PKR | Successful MF	0.01	Beta	0.00 to 0.01
No further repair | MF repair	0.11	Beta	0.08 to 0.13
No further repair | Successful MF repair	0.55	Beta	0.44 to 0.66
First TKR/PKR | Successful MF repair	0.01	Beta	0.00 to 0.01
First TKR/PKR | No further repair	0.01	Beta	0.00 to 0.01
Clinical: TKR			
Further KR | First TKR/PKR	0.01	Beta	0.00 to 0.01
No further KR | First TKR/PKR	0.00	Beta	0
Further KR | Successful first TKR/PKR	0.01	Beta	0.009 to 0.013
No further KR | Successful first TKR/PKR	0.02	Beta	0.01 to 0.02
No further KR | Further KR	0.02	Beta	0.02 to 0.03
Further KR | Successful further KR	0.01	Beta	0.009 to 0.013
No further KR | Successful further KR	0.02	Beta	0.01 to 0.02
Ratio of TKR:PKR	0.50	Beta	0.40 to 0.60
Procedure mortality, TKR1	0.01	Beta	0.006 to 0.008
Procedure mortality, TKR2	0.01	Beta	0.009 to 0.013
HRQoL			
HRQoL before primary repair	0.65	Beta	0.52 to 0.78
HRQoL, Primary ACI (Spherox, MACI, ChondroCelect), yr 1	0.76	Beta	0.61 to 0.91
HRQoL, Primary ACI (Spherox, MACI, ChondroCelect), yr 2+	0.82	Beta	0.65 to 0.98
HRQoL, Primary MF, yr 1	0.76	Beta	0.61 to 0.91
HRQoL, Primary MF, yr 2-4	0.82	Beta	0.65 to 0.98
HRQoL, Primary MF, yr5	0.65	Beta	0.52 to 0.78
HRQoL, Before 2nd repair	0.65	Beta	0.52 to 0.78
HRQoL, No 2nd repair	0.69	Beta	0.55 to 0.83
HRQoL, ACI | 1st ACI, yr 1	0.76	Beta	0.61 to 0.91
HRQoL, ACI | 1st ACI, yr 2+	0.82	Beta	0.65 to 0.98
HRQoL, MF | 1st ACI, yr 1	0.76	Beta	0.61 to 0.91
HRQoL, MF | 1st ACI, yr 2-4	0.82	Beta	0.65 to 0.98
HRQoL, MF | 1st ACI, yr 5	0.65	Beta	0.52 to 0.78
HRQoL, ACI | 1st MF, yr 1	0.76	Beta	0.61 to 0.91
HRQoL, ACI | 1st MF, yr 2-3	0.82	Beta	0.65 to 0.98
HRQoL, ACI | 1st MF, yr 4-5	0.79	Beta	0.63 to 0.95
HRQoL, MF | 1st MF, yr 1	0.76	Beta	0.61 to 0.91
HRQoL, MF | 1st MF, yr 2-4	0.82	Beta	0.65 to 0.98
HRQoL, MF | 1st MF, yr 5	0.65	Beta	0.52 to 0.78
HRQoL, No further repair	0.69	Beta	0.55 to 0.83
HRQoL, Before 1st KR	0.62	Beta	0.49 to 0.74
HRQoL, Successful 1st KR | TKR/PKR	0.78	Beta	0.62 to 0.94
HRQoL, Before 2nd KR	0.56	Beta	0.45 to 0.67
HRQoL, Successful 2nd KR	0.78	Beta	0.62 to 0.94
HRQoL, No further KR	0.69	Beta	0.55 to 0.83

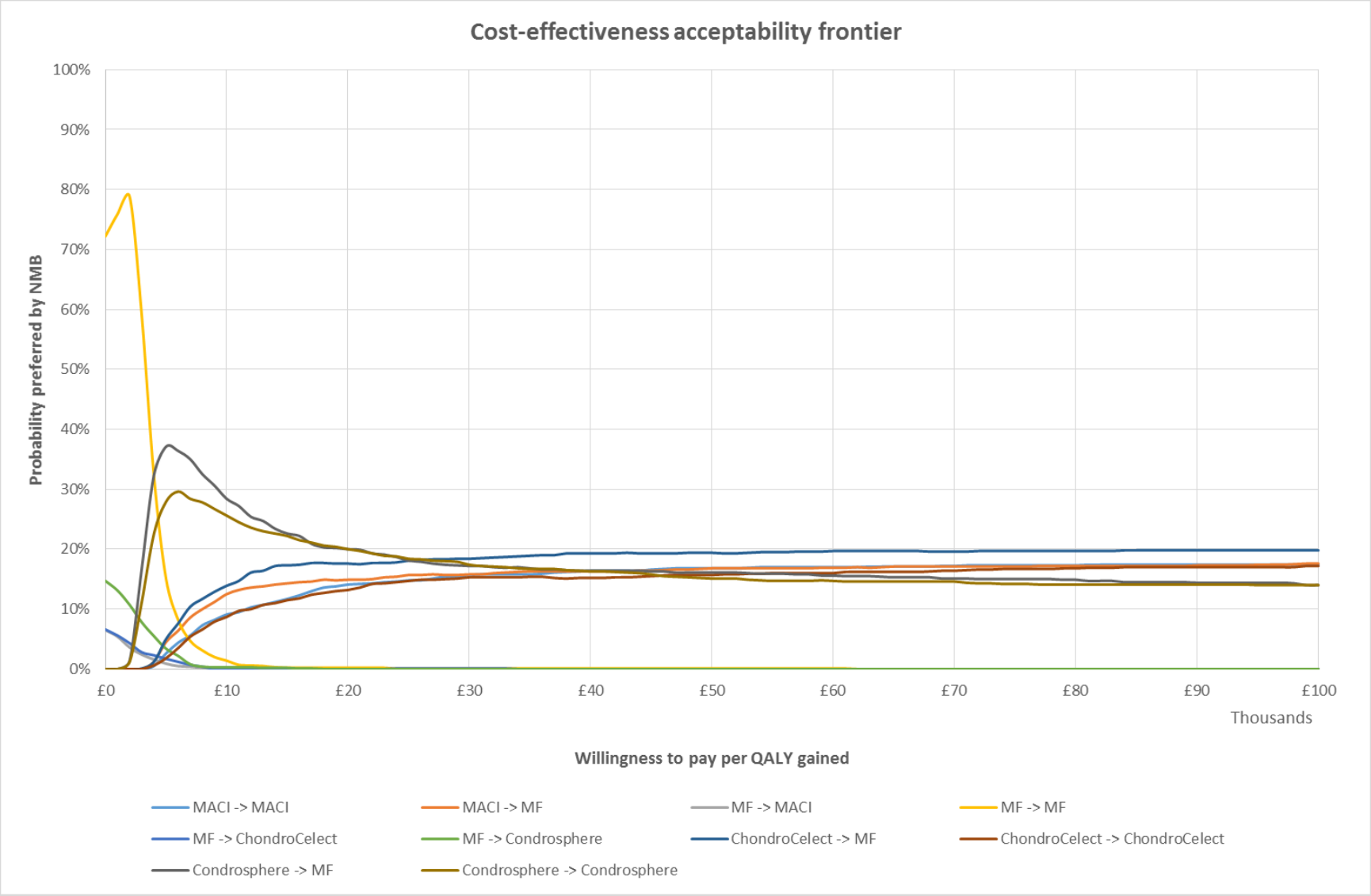
The results of the PSA are presented in terms of net monetary benefit (NMB) at a WTP threshold of £20,000 per QALY.

The tabulated PSA results (Table 63) give the probability (%) of each treatment pathway being preferred by NMB at WTP of £20,000. The results show that Spherox followed by MF and Spherox followed by Spherox have the highest probability (each 20%). The CEAF (Figure 17) gives a graphical representation of the probability of being preferred by NMB for all comparators at varying WTP thresholds up to £100,000. At the £20,000 threshold on the X-axis, Spherox followed by MF and Spherox followed by Spherox are shown at 20% probability (Y-axis).

Table 63. PSA results

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)	Preferred by NMB
MF -> MF	£5,572	15.8364	..	..	..	0.2%
MF -> Spherox	£6,848	15.8458			Ext. Dominated	0.0%
MF -> MACI	£7,811	15.8355			Dominated	0.0%
MF -> ChondroCelect	£7,848	15.8374			Dominated	0.0%
Spherox -> MF	£14,041	17.9756	£8,469	2.1392	£3,959	20.0%
Spherox -> Spherox	£14,698	17.9905			Ext. Dominated	20.0%
MACI -> MF	£20,389	18.1668	£6,348	0.1912	£33,206	14.9%
ChondroCelect -> MF	£20,451	18.1509			Dominated	17.6%
MACI -> MACI	£21,655	18.1694	£1,266	0.0027	£476,769	14.1%
ChondroCelect -> ChondroCelect	£22,006	18.1407			Dominated	13.2%
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval						

Figure 17. Cost effectiveness acceptability frontier



Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) was performed on Spherox followed by MF versus MF followed by MF. Parameter values were varied by 20%.

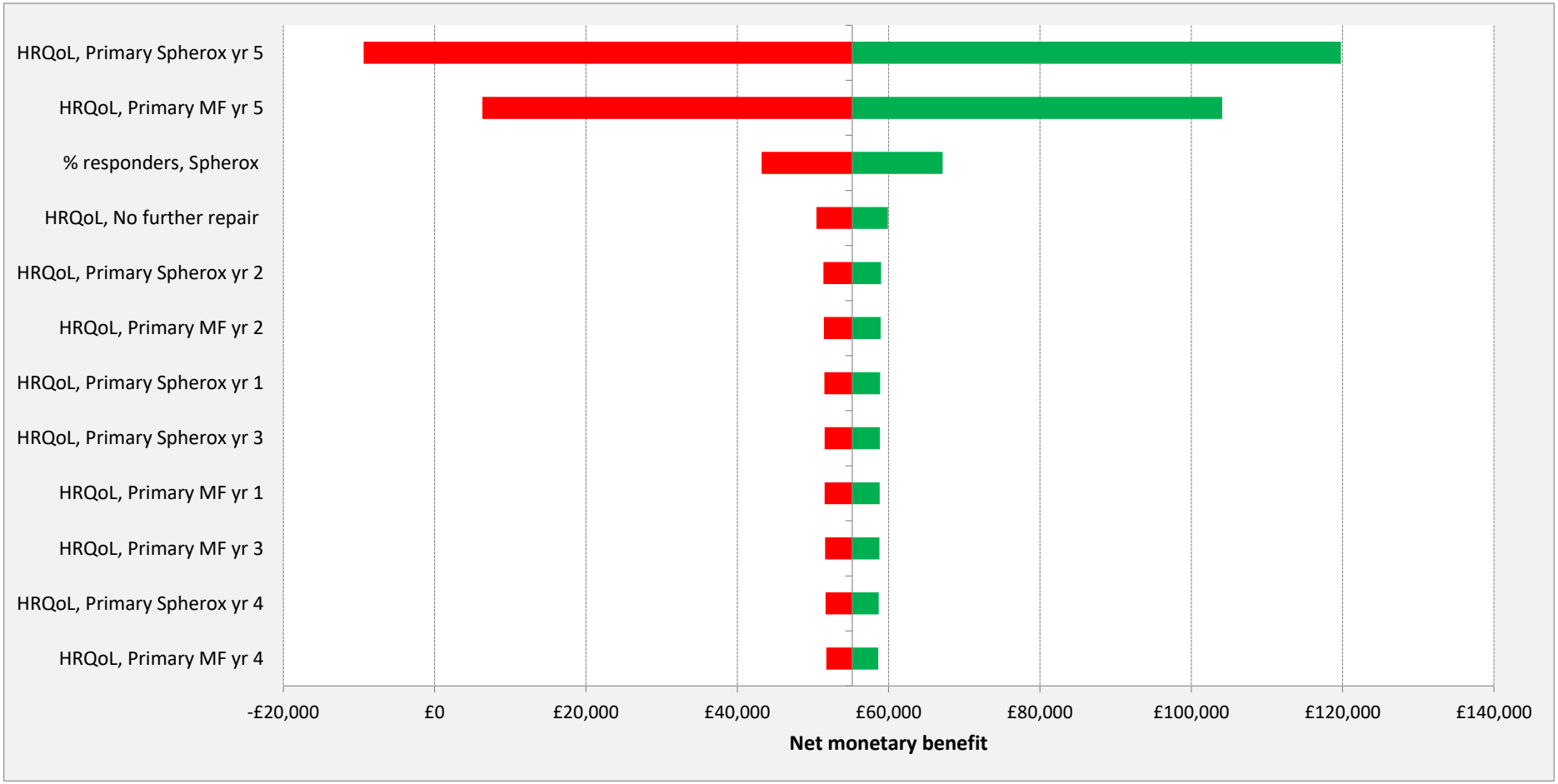
The DSA is presented in terms of net monetary benefit (NMB) at a WTP threshold of £20,000 per QALY. – the most significant drivers are listed from top to bottom.

Table 64 provides the results of the DSA with the most significant drivers listed from bottom to top. A tornado plot (Figure 18) of the most sensitive parameters is used to illustrate the results of the analysis – the most significant drivers are listed from top to bottom.

Table 64. Deterministic sensitivity analysis results

	Variation (20%)		NMB		Change from baseline NMB	
Parameter	**Low**	**High**	**Low**	**High**	**Lower change**	**Upper change**
HRQoL, Primary Spherox yr 4	0.6536	0.9804	£31,649	£36,318	-£2,335	£2,335
HRQoL, Primary MF yr 3	0.6536	0.9804	£31,592	£36,375	-£2,392	£2,392
HRQoL, Primary MF yr 1	0.608	0.912	£31,554	£36,413	-£2,429	£2,429
HRQoL, Primary Spherox yr 3	0.6536	0.9804	£31,550	£36,418	-£2,434	£2,434
HRQoL, Primary Spherox yr 1	0.608	0.912	£31,523	£36,444	-£2,460	£2,460
HRQoL, Primary MF yr 2	0.6536	0.9804	£31,484	£36,483	-£2,499	£2,499
HRQoL, Primary Spherox yr 2	0.6536	0.9804	£31,446	£36,521	-£2,537	£2,537
Cost, Spherox	10580.52	15870.78	£31,338	£36,629	-£2,645	£2,645
HRQoL, No further repair	0.5528	0.8292	£30,840	£37,127	-£3,144	£3,144
% responders, Spherox	0.648	0.972	£26,044	£41,923	-£7,940	£7,940
HRQoL, Primary MF yr 5	0.5232	0.7848	£1,397	£66,570	-£32,586	£32,586
HRQoL, Primary Spherox yr 5	0.6536	0.9804	-£9,067	£77,034	-£43,050	£43,050

Figure 18. Tornado diagram: Spherox followed by MF vs. MF followed by MF



Scenario analyses

Scenario 1 – Varying time horizons

The model time horizon was changed from lifetime (approximately 67 years) to 5, 15, and 25 years. Full incremental results are shown below.

Table 65. Time horizon – 5 Years

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£4,785	3.5324	..	..	..
MF -> Spherox	£5,299	3.5323			Dominated
MF -> ChondroCelect	£5,673	3.5318			Dominated
MF -> MACI	£5,673	3.5318			Dominated
Spherox -> MF	£13,308	3.6455	£8,524	0.1131	£75,395
Spherox -> Spherox	£13,468	3.6455			Dominated
MACI -> MF	£19,645	3.6763	£6,337	0.0308	£205,579
ChondroCelect -> MF	£19,691	3.6757			Dominated
MACI -> MACI	£19,940	3.6762			Dominated
ChondroCelect -> ChondroCelect	£20,137	3.6755			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Table 66. Time horizon – 15 Years

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£4,991	8.2881	..	..	..
MF->Spherox	£5,902	8.2883			Ext.Dominated
MF->ChondroCelect	£6,564	8.2870			Dominated
MF -> MACI	£6,564	8.2869			Dominated
Spherox -> MF	£13,463	9.2852	£8,472	0.9971	£8,497
Spherox -> Spherox	£13,921	9.2854			Ext. Dominated
MACI -> MF	£19,811	9.3663	£6,348	0.0812	£78,218
ChondroCelect -> MF	£19,856	9.3631			Dominated
MACI -> MACI	£20,659	9.3658			Dominated
ChondroCelect -> ChondroCelect	£20,853	9.3625			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Table 67. Time horizon – 25 Years

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)

MF -> MF	£5,223	11.5835	..	..	..
MF -> Spherox	£6,382	11.5838			Ext. Dominated
MF -> ChondroCelect	£7,225	11.5820			Dominated
MF -> MACI	£7,225	11.5819			Dominated
Spherox -> MF	£13,666	13.1459	£8,443	1.5624	£5,404
Spherox -> Spherox	£14,314	13.1462			Ext. Dominated
MACI -> MF	£20,021	13.2594	£6,355	0.1135	£55,988
ChondroCelect -> MF	£20,065	13.2544			Dominated
MACI -> MACI	£21,223	13.2586			Dominated
ChondroCelect -> ChondroCelect	£21,416	13.2536			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Scenario 2 – Varying proportion of PKR

The proportion of PKR was set to 0% (no PKR - Table 68) and 100% (all PKR - Table 69). Full incremental results are shown below.

Table 68. No partial knee replacement as first

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,764	15.8533	..	..	..
MF -> Spherox	£7,157	15.8537			Ext. Dominated
MF -> ChondroCelect	£8,169	15.8515			Dominated
MF -> MACI	£8,169	15.8514			Dominated
Spherox -> MF	£14,183	17.9734	£8,419	2.1201	£3,971
Spherox -> Spherox	£15,018	17.9739			Ext. Dominated
MACI -> MF	£20,545	18.1191	£6,362	0.1457	£43,676
ChondroCelect -> MF	£20,589	18.1124			Dominated
MACI -> MACI	£22,092	18.1180			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1113			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Table 69. All partial knee replacement as first

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,762	15.8487	..	..	..
MF -> Spherox	£7,154	15.8491			Ext. Dominated
MF -> ChondroCelect	£8,167	15.8467			Dominated
MF -> MACI	£8,167	15.8467			Dominated
Spherox -> MF	£14,181	17.9688	£8,419	2.1201	£3,971
Spherox -> Spherox	£15,016	17.9693			Ext. Dominated
MACI -> MF	£20,543	18.1145	£6,362	0.1457	£43,676

ChondroCelect -> MF	£20,587	18.1078			Dominated
MACI -> MACI	£22,089	18.1134			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1067			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Scenario 3 – Varying utilities

Utility assumptions were varied according to scenarios tested in Mistry et al (32). Full incremental results are shown below.

The first assumption to be tested was the utility for patients that do not have a second repair following primary repair. In the base case this was 0.691, and in the scenario we changed to 0.654 (utility for failure).

Table 70. Utility of no further repair equal to failure

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,762	15.7154	..	..	..
MF -> Spherox	£7,154	15.7158			Ext. Dominated
MF -> ChondroCelect	£8,167	15.7136			Dominated
MF -> MACI	£8,167	15.7134			Dominated
Spherox -> MF	£14,181	17.8158	£8,419	2.1004	£4,008
Spherox -> Spherox	£15,016	17.8163			Ext. Dominated
MACI -> MF	£20,543	18.0095	£6,362	0.1937	£32,838
ChondroCelect -> MF	£20,587	18.0086			Dominated
MACI -> MACI	£22,089	18.0084			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.0075			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

The second assumption to be tested was the utility after failure (utility before second repair). In base case this was 0.654, and in the scenario we changed to 0.817 (utility for success).

Table 71. Utility for failure equal to success

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,763	15.8775	..	..	..

MF -> Spherox	£7,156	15.8779			Ext. Dominated
MF -> ChondroCelect	£8,168	15.8756			Dominated
MF -> MACI	£8,168	15.8755			Dominated
Spherox -> MF	£14,182	17.9870	£8,419	2.1095	£3,991
Spherox -> Spherox	£15,017	17.9876			Ext. Dominated
MACI -> MF	£20,544	18.1338	£6,362	0.1468	£43,333
ChondroCelect -> MF	£20,588	18.1288			Dominated
MACI -> MACI	£22,091	18.1328			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1277			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

The third assumption to be tested was using the midpoint of utilities used in the two scenarios (0.746) for the utility of failure.

Table 72. Utility for failure equal to success

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,763	15.8659	..	..	..
MF -> Spherox	£7,156	15.8663			Ext. Dominated
MF -> ChondroCelect	£8,168	15.8641			Dominated
MF -> MACI	£8,168	15.8640			Dominated
Spherox -> MF	£14,182	17.9801	£8,419	2.1142	£3,982
Spherox -> Spherox	£15,017	17.9806			Ext. Dominated
MACI -> MF	£20,544	18.1264	£6,362	0.1463	£43,481
ChondroCelect -> MF	£20,588	18.1207			Dominated
MACI -> MACI	£22,091	18.1253			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1200			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

The fourth utility assumption to be tested was that patient utility dropped at year 5 following MF. We changed from 0.654 to 0.817, the same for ACIs (except ACI following MF).

Table 73. Changing Year 5+ Utility for MF

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,763	17.8827	..	..	..
MF -> Spherox	£7,156	17.8818			Dominated
MF -> ChondroCelect	£8,168	17.8796			Dominated
MF -> MACI	£8,168	17.8795			Dominated
Spherox -> MF	£14,182	17.9719			Ext. Dominated
Spherox -> Spherox	£15,017	17.9717			Dominated
MACI -> MF	£20,544	18.1176	£14,781	0.2349	£62,927

ChondroCelect -> MF	£20,588	18.1111			Dominated
MACI -> MACI	£22,091	18.1157			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1090			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

The fifth utility assumption to be tested was the utility before second TKR. This was changed from 0.557 to 0.615, equal to the utility before first TKR.

Table 74. Utility before second TKR equal to before first TKR

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,763	15.8581	..	..	..
MF -> Spherox	£7,156	15.8585			Ext. Dominated
MF -> ChondroCelect	£8,168	15.8562			Dominated
MF -> MACI	£8,168	15.8561			Dominated
Spherox -> MF	£14,182	17.9782	£8,419	2.1201	£3,971
Spherox -> Spherox	£15,017	17.9787			Ext. Dominated
MACI -> MF	£20,544	18.1239	£6,362	0.1457	£43,676
ChondroCelect -> MF	£20,588	18.1172			Dominated
MACI -> MACI	£22,091	18.1228			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1161			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

<u>Scenario 4 – Varying cost of Spherox</u>

We tested changing the second procedure performed for Spherox (arthroscopy) to arthrotomy which increases the total cost of Spherox.

Table 75. Varying cost of Spherox

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,763	15.8581	..	..	..
MF -> Spherox	£7,209	15.8585			Ext. Dominated
MF -> ChondroCelect	£8,168	15.8562			Dominated
MF -> MACI	£8,168	15.8561			Dominated
Spherox -> MF	£14,513	17.9782	£8,750	2.1201	£4,127
Spherox -> Spherox	£15,379	17.9787			Ext. Dominated
MACI -> MF	£20,544	18.1239	£6,031	0.1457	£41,405
ChondroCelect -> MF	£20,588	18.1172			Dominated
MACI -> MACI	£22,091	18.1228			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1161			Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval

Scenario 5 – Equivalence efficacy between Spherox and MF

Efficacy values for MF were tested making MF as effective as Spherox. Number of responders and failure rate were changed one per time and results are reported below.

Table 76. Number of responders equal between Spherox and MF

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,890	15.8643	..	..	..
MF -> Spherox	£7,529	15.8651			Ext. Dominated
MF -> ChondroCelect	£8,720	15.8625			Dominated
MF -> MACI	£8,720	15.8624			Dominated
Spherox -> MF	£14,182	17.9710	£8,292	2.1067	£3,936
Spherox -> Spherox	£15,017	17.9717			Ext. Dominated
MACI -> MF	£20,544	18.1166	£6,362	0.1456	£43,680
ChondroCelect -> MF	£20,588	18.1099			Dominated
MACI -> MACI	£22,091	18.1157			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1090			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Table 77. Failure rate equal between Spherox and MF

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER cost per QALY gained (£/QALY)
MF -> MF	£5,469	15.8256	..	..	..
MF -> Spherox	£6,293	15.8258			Ext. Dominated
MF -> ChondroCelect	£6,893	15.8245			Dominated
MF -> MACI	£6,893	15.8245			Dominated
Spherox -> MF	£14,182	17.9711	£8,713	2.1455	£4,061
Spherox -> Spherox	£15,017	17.9716			Ext. Dominated
MACI -> MF	£20,544	18.1168	£6,362	0.1457	£43,676
ChondroCelect -> MF	£20,588	18.1101			Dominated
MACI -> MACI	£22,091	18.1157			Dominated
ChondroCelect -> ChondroCelect	£22,283	18.1090			Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Summary of sensitivity analyses results

PSA was conducted using a WTP of £20,000 and was based on 1,000 simulations. The PSA results showed that Spherox followed by MF and Spherox followed by Spherox have the highest probability of being preferred by NMB.

DSA was conducted using a WTP of £20,000 and was based on varying each parameter value by 20%. The DSA results showed that the top three drivers were: (1) the utility for year 5+ following primary repair with Spherox; (2) utility for year 5+ following primary repair with MF; and (3) the proportion of responders to Spherox.

A series of scenario analyses were also conducted. Varying time horizon had a large impact on results and showed that Spherox was most cost-effective at longer time horizons, when the long-term benefits and costs are captured. Varying the proportion of first knee replacements that were partial versus total did not change results. Most of the scenarios for changing utilities did not have a large impact on results except for changing the assumption for Year 5+ following MF. Changing the cost of Spherox to include an arthroscopy plus arthrotomy, rather than two arthroscopies, changed the results minorly.

B.3.9 Subgroup analysis

No subgroup analyses were conducted.

B.3.10 Validation

Validation of cost-effectiveness analysis

As only two year data from COWISI were available for Spherox, and this was used directly in the model to inform the first cycle, any comparison of the model and trial results would be identical. As such the model completely produces the trial results and no further validation was done.

B.3.11 Interpretation and conclusions of economic evidence

A de novo cost effectiveness model was developed based on a model structure adopted in the ongoing MTA of ACIs and used updated inputs. The model uses the output of the indirect comparison to compare treatment sequences involving the use of Spherox with those including other ACIs and microfracture. The base case results show that Spherox followed by microfracture is the cost effective strategy either amongst only microfracture sequences or including other ACI sequences. Compared with microfracture sequences, Spherox results in a greater number of QALYs (17.97 vs. 15.85 per patient) and costs (£14-15,000 vs. £5-7,000), producing an overall cost per QALY gained of £3,971 for Spherox followed by microfracture vs. microfracture followed by microfracture.

When other ACIs are included in the analysis, they become the most expensive but only slightly more effective options, and so, Spherox followed by microfracture remains the cost effective sequence. The other ACI sequences are either dominated by microfracture followed by microfracture or MACI followed by MF. The cost per QALY for Spherox followed by microfracture sequence compared with a microfracture alone sequence is lower than the £20,000 threshold at £3,971. In general, Spherox is associated with lower costs than other ACIs and similarly effective, such that it becomes the cost effective option in the analysis.

Sensitivity analyses show these conclusions are robust. Probabilistic sensitivity analysis shows that the Spherox sequences have the maximum net monetary benefit in the greatest number of iterations. One way sensitivity analysis shows that the model results are sensitive to the utility level assumed in year five, and scenario analyses shows that when this assumption is change the cost per QALY for Spherox followed by microfracture increases.

Overall, the cost effectiveness analysis developed for this submission shows that Spherox is a cost effective use of NHS resources compared with either microfracture or other ACIs, based on current list prices for all comparators. Most scenario or sensitivity analyses show that this conclusion is robust to changes in the assumptions and data used in the model.

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Single technology appraisal

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

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on Tuesday 22nd August 2017 from Co.don AG. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm** on **22 September**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation
Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY QUESTION. Company submission (CS), section B.1.1, table 1 (page 13). The submission included the comparators, microfracture and autologous chondrocyte implantation (ACI, specifically MACI and ChondroCelect). Please substantiate your position on omitting the remaining comparators listed in the scope:

- Traditional ACI
- Knee debridement
- Mosaicplasty
- Best supportive care (non-operative intervention)

Patient access scheme (PAS)

A2. PRIORITY QUESTION. CS, section B.1.2, table 2 (page 16). The submission states "*Previously, a confidential price of* [redacted] *was agreed with the Department of Health but this was specifically for an early access scheme and only relates to unlicensed co.don chondrosphere.*" The list price was used in the submission (CS, Table 52, page 119). Please clarify the company's intentions for the agreed PAS, as per the email request dated 24th August 2017.

Phase 3 trial (NCT01222559; COWISI)

Sample size calculation

A3i. CS, section B.2.4.1 (page 42). The submission states that "*percentages are absolute differences, i.e., percentage points*" and that the lower equivalence bound was taken to be –8.5% for overall Knee Injury and Osteoarthritis Outcome Scores (KOOS).

- CS (page 45) states "*In the second step, the difference between the improvements in overall KOOS after Spherox minus the improvement in overall KOOS after microfracture was tested, with a hypothesised value of zero and a non-inferiority margin of* ***–8.5 points***." Given that KOOS units are not expressed in percentages, please confirm whether the information on page 42 refers to -8.5 rather than 8.5**%**.
- Please provide the rationale for selecting 8.5 rather than 8 to represent a clinically meaningful difference in overall KOOS.

Knee Injury and Osteoarthritis Outcome Scores (KOOS) units

A3ii. CS, page 44. The submission states "*If the lower bound of the one-sided 97.5% confidence interval of the change in overall KOOS at 24 months versus baseline (Day 0) was greater than 10 percentage points ...*"

- Given that KOOS units are not expressed in percentages, please confirm whether this should be '10 points' rather than '10 **percentage** points'.

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- Please confirm that all KOOS data presented in the submission refer to absolute scores.

Baseline characteristics

A4. CS, section B2.3.1 (page 31). The submission states "*the key difference between the arms was in baseline KOOS scale (Spherox [redacted]; MF [redacted])*". Please provide the *p* value for this difference.

A5. Please clarify whether any patients had concomitant surgery in the affected knee such as meniscectomy, osteotomy, ligament repair but not debridement and lavage. If yes, please provide details.

A6. Appendix D, table 84 (page 19) states that [redacted] patients had unspecified previous surgery. Please provide details of these procedures, particularly whether they were to repair the defects or were other interventions that may have damaged the subchondral bone.

Defect size subgroups

A7. PRIORITY QUESTION. CS, section B.2.3.1, table 5 (page 25). The COWISI trial included patients with lesions of defect sizes ≥1cm^2 and <4cm^2. The NICE draft final appraisal determination on "Knee cartilage defects – autologous chondrocyte implantation" recommends ACI for defects over 2cm^2.

- Please clarify the number of patients in COWISI who had defect sizes >2cm^2.
- As in Figure 3 (CS, page 41), please provide the CONSORT flow chart for the subgroup with defect sizes >2cm^2.
- If there are more than 10 participants in the subgroup, please provide the KOOS for the ACI and microfracture arms for the following subgroups:
    - ≤2cm^2 defects
    - >2cm^2 defects

Phase 2 trial

Inadequate spheroid production

A8. CS, section B2.4.2 (page 47). The submission states that "*… predominantly too low doses due to inadequate cell proliferation in culture*". Please clarify what happens to patients for whom there are inadequate spheroids to cover the defect.

Subgroup analysis

A9. Appendix E, Subgroup analysis for phase 2 trial (pages 36-39). There is evidence to suggest that the effectiveness of previous generations of ACI is reduced in people with a

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history of microfracture. Please clarify whether there are data available on treatment success or failure for the following subgroups:

- Duration of injury
- Previous repair attempts involving the subchondral bone

If yes, please provide the data.

Network meta-analysis

Dataset

A10. PRIORITY QUESTION. CS, section B.2.9 (pages 77-79). Please provide the datasets used for the 2 outcomes (number of responders and failure rates) derived from the 3 randomised controlled trials included in the network meta-analysis. Please provide this information in an Excel spreadsheet.

Variance-covariance structure

A11. Please clarify whether the network meta-analysis has a variance-covariance structure for the relative risk estimates. If yes, please:

- provide the variance-covariance structure
- outline why it has not been applied within the probabilistic modelling in the health economic model.

Results

A12. PRIORITY QUESTION. CS, section B.2.9.1, figures 12 and 13 (pages 78 and 79).

- Please clarify whether Figures 12 and 13 present relative risks.
- **Figure 12 Response rates (CS, page 78).**
    - Table 47 (CS, page 112) provides probabilities of response (or risks) of [redacted] for Spherox (chondrosphere) and 86.57% for ChondroCelect. This results in a relative risk of 1.068 (86.57/81.00) which differs from the reported value of 1.209 in Figure 12. Please explain this difference.
    - Please provide the data that underlie Figure 12 in the following format (1 table). The Evidence Review Group assumes that response has been defined as an overall improvement in KOOS of ≥10 points. Please confirm whether this definition is correct. If it is incorrect, please provide the:
        - definition for response that underlies Figure 12
        - data that would result from using a definition of ≥10 point improvement in overall KOOS (1 additional table).

Spherox trial (COWISI)	MACI trial (SUMMIT)	ChondroCelect trial (TIG/ACT)

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	Spherox	MF	MACI	MF	Chondro.	MF
n Resp.	n=???	n=???	n=???	n=???	n=???	n=???
N Patients	N=???	N=???	N=???	N=???	N=???	N=???
T (wks)	T=???	T=???	T=???	T=???	T=???	T=???

n = number of patients responding (numerator)

N = total number of patients (denominator)

T = time period or trial duration that they apply to for the calculation of the response rates

If some numerators are zero, please indicate what has been assumed for these in the network meta-analysis.

If T differs between the trials please provide an account of how this has been handled.

- **Figure 13 Failure rates (CS, page 79).**
  - The values along the x-axis for Figure 13 are in 1000s. Please clarify whether this is correct. If incorrect, please provide correct data.
  - CS, page 78 states that "*The median RRs suggest that Spherox is associated with a lower failure rate compared with MF and ChondroCelect and with a same number of failures compared with MACI (no failures were observed in COWISI and SUMMIT).*" Please clarify how the median RRISK of 0.9894 was calculated for MACI vs. Spherox when there were no failures at 2 years in SUMMIT and COWISI.
  - Please provide the data that underlie Figure 13 in the following format (1 table). The Evidence Review Group assumes that failure has been defined as requiring further surgery. Please confirm whether this definition is correct. If it is incorrect, please provide the definition for failure that underlies Figure 13.

	Spherox trial (COWISI)		MACI trial (SUMMIT)		ChondroCelect trial (TIG/ACT)	
	Spherox	MF	MACI	MF	Chondro.	MF
n Fail	n=???	n=???	n=???	n=???	n=???	n=???
N Patients	N=???	N=???	N=???	N=???	N=???	N=???
T (wks)	T=???	T=???	T=???	T=???	T=???	T=???

n = number of patients not responding (numerator)

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N = total number of patients (denominator)

T = time period or trial duration that they apply to for the calculation of the response rates

If some numerators are zero, please indicate what has been assumed for these in the network meta-analysis.

If T differs between the trials please provide an account of how this has been handled.

Section B: Clarification on cost-effectiveness data

Technology

Costs

B1. PRIORITY QUESTION. CS, section B.3.5, table 52 (page 119). The submission states that unit cost for Spherox cells is £10,000 per culture. Please clarify whether the cost includes all elements between harvest and implantation, for example, courier costs, for each patient.

B2. CS, section B2.4.2 (page 47). As stated in the submission, there are situations when there is no or only inadequate cell growth. Please clarify the costs to the NHS in these circumstances, for example harvesting arthroscopy.

Expired products

B3. PRIORITY QUESTION. Appendix C, Summary of product characteristics (page 8). The SmPC states that the shelf life for Spherox is 72 hours. Please clarify what happens if implantation has to be deferred for weeks or months. For example, are there cases when a second biopsy and culture are necessary?

Table 47 Clinical inputs (CS, page 112)

Spherox (chondrosphere)

B4. PRIORITY QUESTION. At the central estimates of the deterministic analysis in Table 47, Spherox has a lower response rate than MACI and ChondroCelect and the same repair rates as MACI. However, in Table 60 (CS, page 133), higher total quality-adjusted life-years (QALYs) for microfracture (MF)→Spherox are reported than with MF→ChondroCelect and MF→MACI. Please provide the intuition behind this difference.

Microfracture (MF)

B5. PRIORITY QUESTION. At the central estimates of the deterministic analysis in Table 47, microfracture has a lower response rate than Spherox, MACI and ChondroCelect and higher repair rates. In reference to Table 60 (CS, page 133), please provide the intuition behind:

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- The higher total QALYs for Spherox→Spherox compared to Spherox→MF
- The lower total QALYs for MACI→MACI compared to MACI→MF
- The lower total QALYs for ChondroCelect→ChondroCelect compared to ChondroCelect→MF

Annual transition probabilities

Table 48 (CS, page 113)

B6. In Table 48 (CS, page 113), please explain the meaning of 'Successful primary' in the second row. For example, column 2, row 2, a transition probability for a 'Successful primary' is given as 0.4437. Does this imply that all initially successful first repairs will have 44% long-term success, whereas 55% will be unsuccessful and will not have a second repair?

Table 50 (CS, page 115)

B7. Please itemise the sources of the probabilities in Table 50, including full table or page referencing.

Excel model

B8. The columns AT ('Failed 1st TKR') and AU ('Failed 1st PKR') of the cohort flows are associated with utility values in row 19 of 0.691. The columns AV ('Successful KR') and AW ('Successful 1st KR') of the cohort flows are associated with utility values in row 19 of 0.557. This seems counter intuitive. Please clarify whether the columns have been mislabelled or incorrect utility values applied. If incorrect, please provide correct data. If correct, please outline the rationale for this.

B9. CS, section B.3.3, Table 47 (page 112). Please clarify how the value of 1.13 in the last row of the last column, labelled 'ChondroCelect (%)*' was derived. Please also indicate where this value appears in the Excel model.

<u>Section C: Textual clarifications and additional points</u>

C1. Document '[ID851] chondrosphere - CSR_HS13 24mo_Final Assessment - 220817 [ACIC]' (page 3) states that [redacted]

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]

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C2. Document '2017appendix_16.1.1' (pages 231-232) states [redacted]

- [redacted]

C3. CS, section B.1.3 (page 19). The submission states that "*Spherox treatment application is less invasive than other ACIs, resulting in lower healthcare resource utilization and providing similar or greater health benefits at a lower cost than other ACIs or ACI technologies.*"

- Please clarify in what way the Spherox application is less invasive, for example, undertaken via mini-arthrotomy or arthroscopy.
- Please provide the average time taken for each of these procedures, that is arthrotomy, arthroscopy etc.
- Please clarify whether the time taken in these procedures affect spheroid viability.

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Single technology appraisal

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

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on Tuesday 22nd August 2017 from Co.don AG. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm** on **22 September**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
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Encl. checklist for confidential information

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The Company has provided written responses to the clarification questions in blue italicized text directly below each question. Additional documents (e.g. spreadsheets, publications) referenced in the responses were submitted along with this response document to NICE.

Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY QUESTION. Company submission (CS), section B.1.1, table 1 (page 13). The submission included the comparators, microfracture and autologous chondrocyte implantation (ACI, specifically MACI and ChondroCelect). Please substantiate your position on omitting the remaining comparators listed in the scope:

- Traditional ACI
- Knee debridement
- Mosaicplasty
- Best supportive care (non-operative intervention)

Based on market research conducted by the Company, MF was considered the most relevant comparator and is the most widely used in the NHS to treat knee cartilage damage. The other comparators, listed below, were not considered in the analysis for the following reasons:

- *Traditional ACI: This intervention is not routinely available in the UK. It is only carried out under hospital exemption on a non-routine basis by Oscell at the Robert Agnes NHS Centre.*
- *Knee debridement: This intervention is more likely to be used before or after ACI or MF in the treatment pathway.*
- *Mosaicplasty: This intervention is only used in 6-7% of knee cartilage lesions in current clinical practice in the NHS, and when it is used, it is usually considered when symptoms persist after an ACI or MF rather than as an alternative to ACI.*
- *Best supportive care (non-operative intervention including physiotherapy): This is used before surgical intervention and is not an alternative to either ACI or MF.*

In addition, apart from mosaicplasty, none of the above interventions are recommended in NICE guidance. As for the guidance on mosaicplasty, it was produced through the interventional procedures guidance process (IPG162).

Patient access scheme (PAS)

A2. PRIORITY QUESTION. CS, section B.1.2, table 2 (page 16). The submission states "*Previously, a confidential price of* [redacted] *was agreed with the Department of Health but this was specifically for an early access scheme and only relates to unlicensed co.don chondrosphere.*" The list price was used in the submission (CS, Table 52, page 119). Please clarify the company's intentions for the agreed PAS, as per the email request dated 24th August 2017.

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[redacted]

Phase 3 trial (NCT01222559; COWISI)

Sample size calculation

A3i. CS, section B.2.4.1 (page 42). The submission states that "*percentages are absolute differences, i.e., percentage points*" and that the lower equivalence bound was taken to be –8.5% for overall Knee Injury and Osteoarthritis Outcome Scores (KOOS).

- CS (page 45) states "*In the second step, the difference between the improvements in overall KOOS after Spherox minus the improvement in overall KOOS after microfracture was tested, with a hypothesised value of zero and a non-inferiority margin of **–8.5 points***." Given that KOOS units are not expressed in percentages, please confirm whether the information on page 42 refers to -8.5 rather than 8.5**%**.

The primary endpoint is defined as change in overall KOOS from baseline to final assessment at 24 months. The individual sums of the 5 sub-scores (pain; symptoms; function in daily living; function in sport and recreation; and quality of life) are transformed to a scale of 0 to 100 points, with 0 representing extreme knee problems and 100 representing no knee problems. The overall KOOS is the mean of all KOOS sub-scores. Therefore the result lies in a range from [0-100]. According to Roos et al. 2003, scores between 0 and 100 represent the percentage of total possible score achieved, therefore they confirmed that the score is a percentage score from 0 to 100 (Roos et al. 2003; publication submitted with this ERG response). Therefore the study documents, e. g. the protocol, comprised these definitions. The actual statistical analysis for the primary and secondary endpoints for the KOOS score, e. g. changes from baseline to the follow up visit, or respectively comparisons of Spherox vs. MF, is based on the assessment of points. Thus a clear definition of the endpoints with regard to the change is only possible with points. Thus the information on page 42 of the submission does refer to -8.5 rather than 8.5%.

- Please provide the rationale for selecting 8.5 rather than 8 to represent a clinically meaningful difference in overall KOOS.

As described in the study protocol, the statistical hypotheses will be tested hierarchically. First, the relevant clinical improvement of Spherox versus baseline has to be shown. In case the lower bound of the one-sided 97.5% confidence interval of the change in overall KOOS at 24 months versus baseline is greater than 10 percent points (Roos et al. 1998; publication submitted with this ERG response), the relevant clinical improvement is shown, and the non-inferiority test of Spherox in comparison to MF will be performed. An assumed difference between Spherox minus MF of zero will be evaluated with a non-inferiority margin of -8.5 points (difference of both treatments, Spherox minus MF).

One should note that the study was planned in 2010 and the reference publication was Saris et al. 2008 (publication submitted with this ERG response) where a non-inferiority margin of -9 is given: "Non-inferiority for the overall KOOS was defined as having been demonstrated if the lower end of the 95% confidence interval for the difference between adjusted means in the 2 treatment groups was above –9 percentage points."

In general, for the non-inferiority margins, values smaller than minimal clinically important difference (MCID) should be chosen on the one hand (values of about 10). According to Roos et al, 2003, a level of 10 points or more of improvement or decline was suggested as a cut-off representing a clinically significant difference. Furthermore the user guide from the KOOS

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website (http://www.koos.nu/) stated that the Minimal Important Change (MIC) is currently suggested to be 8-10. However, to determine the minimum sample size required, the non-inferiority margin smaller than but near to MCID was chosen. The value of -8.5 takes into account both considerations and is stricter than the margin used in the reference trial by Saris et al, 2008.

Knee Injury and Osteoarthritis Outcome Scores (KOOS) units

A3ii. CS, page 44. The submission states "*If the lower bound of the one-sided 97.5% confidence interval of the change in overall KOOS at 24 months versus baseline (Day 0) was greater than 10 percentage points ...*"

- Given that KOOS units are not expressed in percentages, please confirm whether this should be '10 points' rather than '10 **percentage** points'.

*Roos et al, 2003 stated that a level of 10 points or more of improvement or decline was suggested as a cut-off representing a clinically significant difference. The minimal perceptible clinical improvement (MPCI) represents the difference on the measurement scale associated with the smallest change in the health status detectable by the patient. Therefore the study protocol comprised these definitions. The statistical analysis is based on the assessment of **points**, the relevant clinical improvement at 24 month in comparison to baseline is shown in case of a lower confidence bound greater than 10 **points**. Changes from baseline to the follow up visit, or respectively comparisons Spherox vs. MF, are based on the evaluation of the points.*

As stated in the CSR, the primary analysis reveals for the test for relevant clinical improvement from baseline to Visit 6, 24 months after treatment, for the Spherox group:

- *Difference = [redacted] (confidence interval (CI) [redacted]), p < 0.0001*

*This difference should be interpreted as **points**.*

- Please confirm that all KOOS data presented in the submission refer to absolute scores.

Correct, the actual statistical analysis for the overall KOOS and its 5 sub-scores is based on the assessment of points.

Baseline characteristics

A4. CS, section B2.3.1 (page 31). The submission states "*the key difference between the arms was in baseline KOOS scale (Spherox [redacted]; MF [redacted])*". Please provide the *p* value for this difference.

The Satterthwaite t-test was performed to investigate the KOOS baseline level scale for Spherox versus MF; the p-value was [redacted].

A5. Please clarify whether any patients had concomitant surgery in the affected knee such as meniscectomy, osteotomy, ligament repair but not debridement and lavage. If yes, please provide details.

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No concomitant surgeries were conducted.

A6. Appendix D, table 84 (page 19) states that [redacted] patients had unspecified previous surgery. Please provide details of these procedures, particularly whether they were to repair the defects or were other interventions that may have damaged the subchondral bone.

The previous surgeries were specified as semitendinosus sinew transplant and semitendinosus gracilis sinew treatment. Dependent on the surgery technique a damage of the subchondral bone can be excluded, as sinew transplants do not affect the weight-bearing area and therefore the treated cartilage area.

Defect size subgroups

A7. PRIORITY QUESTION. CS, section B.2.3.1, table 5 (page 25). The COWISI trial included patients with lesions of defect sizes ≥1cm^2 and <4cm^2. The NICE draft final appraisal determination on "Knee cartilage defects – autologous chondrocyte implantation" recommends ACI for defects over 2cm^2.

- Please clarify the number of patients in COWISI who had defect sizes >2cm^2.

A total of 102 patients with defect sizes ranging from ≥1cm^2 and <4cm^2 were randomised in the COWISI trial (ITT population comprised 48 patients treated with Spherox and 49 patients treated with MF). Of these, [redacted] patients from the Spherox group and [redacted] patients from the MF group had defect sizes >2cm^2 (ITT1).

- As in Figure 3 (CS, page 41), please provide the CONSORT flow chart for the subgroup with defect sizes >2cm^2.

This flow chart is provided below.

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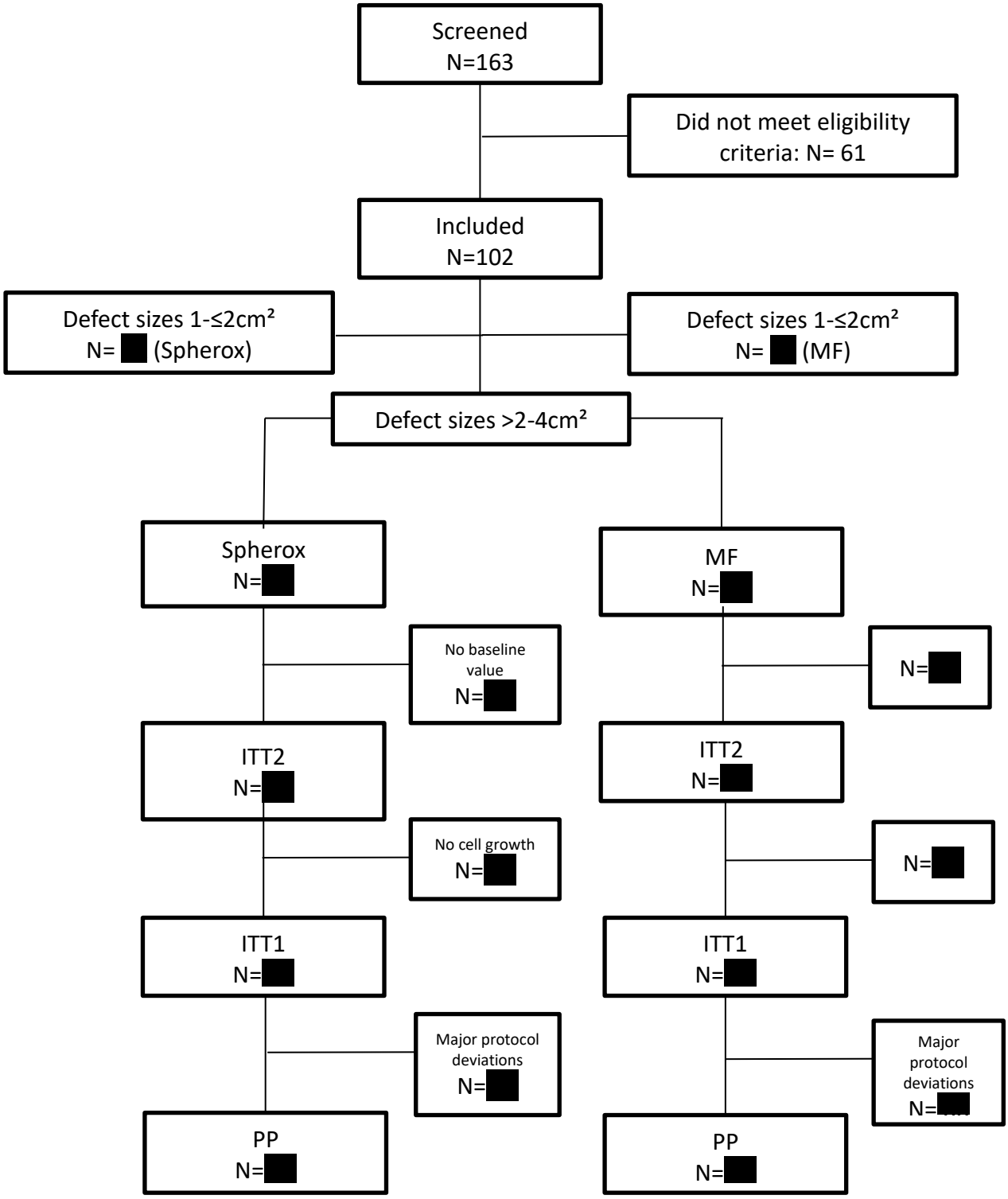

- If there are more than 10 participants in the subgroup, please provide the KOOS for the ACI and microfracture arms for the following subgroups:
    - ≤2cm^2 defects

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- >2cm^2 defects

A subgroup analysis was conducted where the patients were stratified into two classes of defect sizes (1- ≤ 2 cm² and >2-4 cm²). The defect size category 1- ≤ 2 cm² included [redacted] *ITT1 patients in the Spherox group and* [redacted] *patients in the MF group. The defect size category >2-4 cm² included* [redacted] *patients treated with Spherox and* [redacted] *patients treated by MF. Both groups showed an increase in overall KOOS from baseline to Visit 24 months after treatment. At 24 months follow-up, the KOOS values in the defect size group 1- ≤ 2 cm² defects were* [redacted] *for Spherox and* [redacted] *for MF, and the KOOS values in the defect size group >2-4 cm² were* [redacted] *for Spherox and* [redacted] *for MF. The results of the mean KOOS overall score are displayed for baseline and 12 and 24 months follow-up visits in the table below. All within group analysis revealed a statistically significant improvement (p < 0.0001 for both Spherox subgroups 1-2 cm² and 2-4cm² and for MF 1-2 cm² and p =* [redacted] *for the MF subgroup 2-4cm²).*

A T-test (Satterthwaite) was performed and demonstrated non-inferiority of Spherox vis-à-vis MF in both sub-groups (least-square mean difference from baseline for Spherox minus mean difference from baseline for MF):

Strata Defect size: 1-2cm²:

Difference = [redacted] *(p =* [redacted] *) with lower bound of CI equal to* [redacted]*.*

Strata Defect size: 2-4cm²:

Difference = [redacted] *(p =* [redacted] *) with lower bound of CI equal to* [redacted]*.*

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KOOS score	Day before arthroscopy				12 months				24 months			
	Strata Defect size and treatment group				Strata Defect size and treatment group				Strata Defect size and treatment group			
	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²
KOOS (overall)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower quartile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper quartile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower quartile					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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KOOS score	Day before arthroscopy				12 months				24 months			
	Strata Defect size and treatment group				Strata Defect size and treatment group				Strata Defect size and treatment group			
	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²	ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²
Upper quartile					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The following table shows the mean values (± SD) for the change from baseline for all 5 KOOS sub-scores (i.e. pain, symptoms, function in daily living, function in sport and recreation, and quality of life). The results indicate a clear increase over the 24-month period in both treatment groups, with values for the Spherox group showing greater change from baseline than the group treated with MF in all 5 KOOS sub-scores. All these within group comparisons were statistical significant with p values below 0.05, expect for the sub-score "function in daily living" for the MF subgroup 2-4cm² (p = [redacted]).

KOOS score		24 months			
		Strata Defect size and treatment group			
		ACT:1-≤2cm²	MF:1-≤2cm²	ACT:>2-4cm²	MF:>2-4cm²
KOOS sub-score "pain"	Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]
KOOS sub-score "symptoms"	Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]
KOOS sub-score "Function in daily living"	Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]
KOOS sub-score "Function in sport and recreation"	Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]
KOOS sub-score "Quality of life"	Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]

As the table below shows, there was in each case a substantial improvement, ranging from approximately [redacted] points in the Spherox group ([redacted] points in the MF group) to approximately [redacted] points in the Spherox group ([redacted] points in the MF group) in the strata 1-2cm². The improvement ranged from [redacted] to [redacted] points in the Spherox group and [redacted] to [redacted] in the MF group for medium defects sizes >2-4cm².

The Satterthwaite test was also performed to investigate non-inferiority of Spherox vis-à-vis MF gave the following result for the 5 sub-scores:

KOOS Sub-score	1-≤2cm²			>2-4cm²		
Spherox vis-à-vis MF	Difference	Lower CL	p value	Difference	Lower CL	p value
"Pain"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Symptoms"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Function in daily living"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Function in sport and recreation"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Quality of life"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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In each direct comparison the improvement was greater in the Spherox group than in the MF group with statistically significant p values in all cases, except the comparison for the sub-score "function in sport and recreation" for the defect size strata >2-4cm².

Phase 2 trial

Inadequate spheroid production

A8. CS, section B2.4.2 (page 47). The submission states that "… *predominantly too low doses due to inadequate cell proliferation in culture*". Please clarify what happens to patients for whom there are inadequate spheroids to cover the defect.

The phase II trial was designed as a dose confirmation study with three doses (low: 3-7 spheroids/cm², medium: 10-30 spheroids/cm² and high: 40-70 spheroids/cm²). The 48 months follow-up results revealed that no dose response was observed. The dose of the product Spherox is defined as 10-70 spheroids/cm^2 implantation suspension. In the phase II trial, some samples from the high dose group showed a lower cell proliferation in culture and thus a product dose fulfilling the medium dose was transplanted. Thus some patients received lower doses than intended due to their randomisation group, but always a sufficient spheroid dose. The transplanted spheroid dose was always within the specification of 10-70 spheroids/cm^2 and was therefore always adequate to cover the defect.

Subgroup analysis

A9. Appendix E, Subgroup analysis for phase 2 trial (pages 36-39). There is evidence to suggest that the effectiveness of previous generations of ACI is reduced in people with a history of microfracture. Please clarify whether there are data available on treatment success or failure for the following subgroups:

- Duration of injury
- Previous repair attempts involving the subchondral bone

If yes, please provide the data.

Minas et al. 2009 (publication submitted with this ERG response) evaluated the failure rates of ACI conducted after previous treatment with marrow stimulation techniques and the results demonstrate that marrow stimulation techniques, like MF, have a strong negative effect on subsequent cartilage repair with ACI and therefore should be used judiciously in larger cartilage defects that could require future treatment with ACI.

Furthermore the Phase III trial assessed the duration of knee symptoms for both treatment groups Spherox and MF. However, in this trial, previous treatment with ACI in the affected knee was an exclusion criteria. The cut-off value between the long- and short-duration subgroups was 1 year. The KOOS results (mean differences with respective 95% confidence intervals) for the MF group at 24 months after treatment revealed better KOOS values (mean ± SD, [redacted] ± [redacted]; median [redacted]; range [redacted]) for patients with a documented symptom duration of < 1 year compared the symptoms durations > 1 year (mean ± SD, [redacted] ± [redacted]; median [redacted]; range [redacted]). Corresponding results for the Spherox group at Visit 6, 24 months after treatment, were:

- *< 1 year: mean ± SD, [redacted] ± [redacted]; median [redacted]; range [redacted]*

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- *>1 year: mean ± SD, [redacted] ± [redacted]; median [redacted]; range [redacted].*

Network meta-analysis

Dataset

A10. PRIORITY QUESTION. CS, section B.2.9 (pages 77-79). Please provide the datasets used for the 2 outcomes (number of responders and failure rates) derived from the 3 randomised controlled trials included in the network meta-analysis. Please provide this information in an Excel spreadsheet.

The Excel spreadsheet (A10_NMA_DATA) with this dataset was submitted with this response document.

Variance-covariance structure

A11. Please clarify whether the network meta-analysis has a variance-covariance structure for the relative risk estimates. If yes, please:

- provide the variance-covariance structure
- outline why it has not been applied within the probabilistic modelling in the health economic model.

A variance-covariance structure was not generated for the relative risk estimates in the NMA and therefore not incorporated in the probabilistic sensitivity analysis in the model due to time and feasibility.

Results

A12. PRIORITY QUESTION. CS, section B.2.9.1, figures 12 and 13 (pages 78 and 79).

- Please clarify whether Figures 12 and 13 present relative risks.

The figures do present relative risks for both number of responders (figure 12) and failure rate (figure 13).

- **Figure 12 Response rates (CS, page 78).**
    - Table 47 (CS, page 112) provides probabilities of response (or risks) of [redacted]% for Spherox (chondrosphere) and 86.57% for ChondroCelect. This results in a relative risk of 1.068 (86.57/[redacted]) which differs from the reported value of 1.209 in Figure 12. Please explain this difference.

The number reported in Table 47 for ChondroCelect was calculated by applying the relative risk (RR) from the NMA, which for ChondroCelect compared to Spherox was 1.209, to the rate for Spherox and converted to a probability using the following approach:

1. *Spherox rate: -(LN(1-[redacted]%))=1.66*
2. *ChondroCelect rate: 1.66*1.209=2.01*

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3. ChondroCelect probability: 1-EXP(-2.01)=86.57%

- Please provide the data that underlie Figure 12 in the following format (1 table). The Evidence Review Group assumes that response has been defined as an overall improvement in KOOS of ≥10 points. Please confirm whether this definition is correct. If it is incorrect, please provide the:
  - definition for response that underlies Figure 12

The definition of responders (summarised in section 8.2.9.2 of the company submission) varied across trials included in the indirect comparison, making results difficult to compare. The definitions from each trial are as follows:

- *COWISI: A responder was defined as having at least a 10-point improvement in the overall KOOS scale;*
- *SUMMIT: A responder was defined as having at least a 10-point improvement in both the KOOS pain and function subscales*
- *TIG/ACT: A responder was defined as having an increase from baseline in overall KOOS of at least 10 percentage points and/or an increase from baseline of at least 10 percentage points in at least 3 of the 4 KOOS subdomains and/or an improvement from baseline in the degree of knee disorder severity of at least one category or a decrease from baseline of at least 20 percentage points in VAS pain score and/or an improvement in the degree of knee disorder severity of at least one category.*

- data that would result from using a definition of ≥10 point improvement in overall KOOS (1 additional table).

As mention above, the definition of responder varies between trials, with TIG/ACT providing a combined definition not only looking at the improvement of ≥10 point improvement in overall KOOS. In the SUMMIT trial only the pain and function subscale are considered and not the overall KOOS. Therefore, data required by the ERG cannot be provided. In the table below the data used in the submission are reported (note: the outcome definition differs between trials).

The difference in length of follow up between TIG/ACT and the other two trials was identified as a possible bias in the NMA. Unfortunately, data at 24 months for TIG/ACT were not reported for the outcome of interest and so the 36 month data are used in the NMA. Due to the small number of studies included, the Company was not able to perform any type of meta-regression to control for these differences between studies and therefore minimise this potential bias on the final results.

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	Spherox trial (COWISI)		MACI trial (SUMMIT)		ChondroCelect trial (TIG/ACT)	
	Spherox	MF	MACI	MF	ChondroCelect	MF
n Resp.	n=[redacted]	n= [redacted]	n=63	n=49	n=34	n=31
N Patients	N=48	N=49	N=72	N=72	N=41	N=50
T (months)	T=24	T=24	T=24	T=24	T=36	T=36
n = number of patients responding (numerator) N = total number of patients (denominator) T = time period or trial duration that they apply to for the calculation of the response rates						

- **Figure 13 Failure rates (CS, page 79).**
    - The values along the x-axis for Figure 13 are in 1000s. Please clarify whether this is correct. If incorrect, please provide correct data.

The values along the x-axis Figure 13 are in 1000s. This scale was selected so that the large 95% confidence intervals for all the RRs obtained could be shown. The confidence intervals are presented in Figure 13 of the submission document.

    - CS, page 78 states that "*The median RRs suggest that Spherox is associated with a lower failure rate compared with MF and ChondroCelect and with a same number of failures compared with MACI (no failures were observed in COWISI and SUMMIT).*" Please clarify how the median RRISK of 0.9894 was calculated for MACI vs. Spherox when there were no failures at 2 years in SUMMIT and COWISI.

The median RR of 0.9894 was calculated assuming that in each arm 0.5 patients experienced the event. This approach was used per the NICE DSU document (Dias et al. 2016; reference provided with this submission) which recommends this in the case that no events are observed in one arm of the trials. Due to the larger sample size of the SUMMIT trial, a RR in favour of MACI was obtained. However, for the purpose of the economic model, 0 events were assumed for both interventions.

    - Please provide the data that underlie Figure 13 in the following format (1 table). The Evidence Review Group assumes that failure has been defined as requiring further surgery. Please confirm whether this definition is correct. If it is incorrect, please provide the definition for failure that underlies Figure 13.

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Failure was defined as the need for revision surgery. This definition was consistent across all the trials. As for response rate, only data on failure rates at 36 months were available from the TIG/ACT trial and so these were used in the NMA as a proxy for 24 month data. The data underlying Figure 13 are shown below:

	Spherox trial (COWISI)		MACI trial (SUMMIT)		ChondroCelect trial (TIG/ACT)	
	Spherox	MF	MACI	MF	ChondroCelect	MF
n Fail	n=[redacted]	n=[redacted]	n=0	n=2	n=2	n=7
N Patients	N=48	N=49	N=72	N=72	N=41	N=50
T (wks)	T=24	T=24	T=24	T=24	T=36	T=36

n = number of patients not responding (numerator)

N = total number of patients (denominator)

T = time period or trial duration that they apply to for the calculation of the response rates

Section B: Clarification on cost-effectiveness data

Technology

Costs

B1. PRIORITY QUESTION. CS, section B.3.5, table 52 (page 119). The submission states that unit cost for Spherox cells is £10,000 per culture. Please clarify whether the cost includes all elements between harvest and implantation, for example, courier costs, for each patient.

The NHS list price for Spherox of £10,000 is the cost per culture per patient. It is the total cost incurred and includes all elements as per contract for regenerative services:

1. *Cell costs – testing/manufacturing/cultivating/processing*
2. *Logistics/Transportation– safe collection and delivery for biopsy/harvesting and implantation (NB including all courier costs)*

There are no other costs incurred other than the £10,000 total charge for all elements of the service.

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B2. CS, section B2.4.2 (page 47). As stated in the submission, there are situations when there is no or only inadequate cell growth. Please clarify the costs to the NHS in these circumstances, for example harvesting arthroscopy.

For any knee cartilage lesion, an arthroscopy is performed to assess the size of the lesion. If treatment with Spherox is needed, harvesting of the cells is then performed during this procedure. In situations where there may be no or inadequate cell growth to facilitate cultivation after harvesting, due to the quality or quantity of the cells harvested, a repeat arthroscopy would be needed to harvest additional cells.

There would be no additional Spherox related costs incurred to the NHS in these extremely rare instances. The NHS is only invoiced once delivery of Spherox is made.

Expired products

B3. PRIORITY QUESTION. Appendix C, Summary of product characteristics (page 8). The SmPC states that the shelf life for Spherox is 72 hours. Please clarify what happens if implantation has to be deferred for weeks or months. For example, are there cases when a second biopsy and culture are necessary?

If there was a deviation beyond the implantation time-frame (after acceptance of the delivery of the cells for implantation by the hospital) that went beyond the 72 hours shelf life** of the cells for implantation, then the implantation could not take place and these cells discarded. Therefore, a new sample (biopsy) would need to be harvested and the culture process repeated.*

** The time-frame to cells being available for implantation is a maximum period of 55 days from day of harvesting. There is no deferment beyond the 55 days.*

*** The 72 hour shelf life is the period the cells (spheroids) are viable for implantation once delivered to the hospital for implantation.*

Table 47 Clinical inputs (CS, page 112)

Spherox (chondrosphere)

B4. PRIORITY QUESTION. At the central estimates of the deterministic analysis in Table 47, Spherox has a lower response rate than MACI and ChondroCelect and the same repair rates as MACI. However, in Table 60 (CS, page 133), higher total quality-adjusted life-years (QALYs) for microfracture (MF)→Spherox are reported than with MF→ChondroCelect and MF→MACI. Please provide the intuition behind this difference.

The following response applies to B4 and B5.

After investigating this issue, these clarifications raised by the ERG were related to how the trial data was interpreted and applied in the model. Previously, the intervention response rate was used for calculating the transition probabilities for successful repair health states to no repair. However, the response rate was implemented incorrectly. For example:

- *The transition from "Successful primary repair" to "No further repair" was the interventions response rate minus the rate for "Successful primary repair" to "Second repair"*

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- *The transition from "Successful second repair" to "No further repair" was the response rate.*

This resulted in some counterintuitive results (total QALYs for some pathways) given the results of the NMA and the trial data, as the ERG has pointed out. This error has now been corrected in the model, using the same assumption in Mistry et al. 2017 and changing the following data inputs:

- *For the transition from "Successful primary repair" to "No further repair", this is now calculated as the non-response rate (e.g. [redacted]% for Spherox) minus the rate for "Successful primary repair" to "Second repair"*
- *The transition from "Successful second repair" to "No further repair, this is now equal to the non-response rate (e.g. [redacted]% for Spherox)*

These values were converted to probabilities for the model cycle. The results of the base case have been updated following these changes and are presented below. As can be seen from the updated results, the total number of QALYs is highest for MF→MACI and lowest for MF→Spherox, which is consistent with NMA findings that show MACI has the numerically highest response rate and comparable failure rate to Spherox.

Base case results – Spherox vs. currently available technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	*£5,763*	*23.039*	*15.8583*	*..*	*..*	*..*	*..*
MF -> Spherox	*£7,156*	*23.039*	*15.9315*				*Ext. Dominated*
Spherox -> MF	*£14,182*	*23.039*	*17.9762*	*£8,419*	*0.000*	*2.1178*	*£3,975*
Spherox -> Spherox	*£15,017*	*23.039*	*18.0269*	*£835*	*0.000*	*0.0507*	*£16,466*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Base case results – Spherox vs. all technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	*£5,763*	*23.039*	*15.8583*	*..*	*..*	*..*	*..*
MF -> Spherox	*£7,156*	*23.039*	*15.9315*				*Ext. Dominated*
MF -> ChondroCelect	*£8,168*	*23.039*	*15.9350*				*Ext. Dominated*
MF -> MACI	*£8,168*	*23.039*	*15.9351*				*Ext. Dominated*
Spherox -> MF	*£14,182*	*23.039*	*17.9762*	*£8,419*	*0.000*	*2.1178*	*£3,975*
Spherox -> Spherox	*£15,017*	*23.039*	*18.0269*	*£835*	*0.000*	*0.0507*	*£16,466*
MACI -> MF	*£20,544*	*23.039*	*18.1187*				*Ext. Dominated*
ChondroCelect -> MF	*£20,588*	*23.039*	*18.1113*				*Dominated*
MACI -> MACI	*£22,091*	*23.039*	*18.1996*				*Ext. Dominated*
ChondroCelect -> ChondroCelect	*£22,283*	*23.039*	*18.2052*	*£7,266*	*0.000*	*0.1783*	*£40,746*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Microfracture (MF)

B5. PRIORITY QUESTION. At the central estimates of the deterministic analysis in Table 47, microfracture has a lower response rate than Spherox, MACI and ChondroCelect and higher repair rates. In reference to Table 60 (CS, page 133), please provide the intuition behind:

- The higher total QALYs for Spherox→Spherox compared to Spherox→MF
- The lower total QALYs for MACI→MACI compared to MACI→MF
- The lower total QALYs for ChondroCelect→ChondroCelect compared to ChondroCelect→MF

Please see the response to B4 above which also applies to B5. The revised base case results still show that the sequence Spherox→Spherox is associated with more QALYs than Spherox→MF, and this is due to the higher response and lower failure rates associated with Spherox vs. MF. As for the other sequences including either MACI or ChondroCelect, the sequences MACI→MACI and ChondroCelect→ChondroCelect have higher QALYs than MACI→MF and ChondroCelect→MF respectively.

Annual transition probabilities

Table 48 (CS, page 113)

B6. In Table 48 (CS, page 113), please explain the meaning of 'Successful primary' in the second row. For example, column 2, row 2, a transition probability for a 'Successful primary' is given as 0.4437. Does this imply that all initially successful first repairs will have 44% long-term success, whereas 55% will be unsuccessful and will not have a second repair?

Based on issues raised by the ERG in questions B4 and B5, an error was found in the implementation of trial data in the model. As a result, the transition probabilities have changed. As an example, and to aid in the response, the data referred to by the ERG in B6 have been changed as follows:

- *The transition probability for staying in "Successful primary" has changed from 0.4437 to 0.90065 (calculated as 100% minus the probabilities to other health states, which have changed; see next bullet point)*
- *The transition probability for "Successful primary" to "No further repair" has changed from 0.5500 to 0.09308 (now calculated as the non-responders' rate minus the rate for "Successful primary repair" to "Second repair"; see response to B4).*

In the model successful primary repair is defined as (CS, page 106):

- *Successful primary repair can be permanent or temporary. For permanent successful repairs, the first repair works and patients stay in the 'successful primary repair' health state; for temporary successful primary repair, the repair fails after patients are symptom free for years. Patients can then decide to either receive a second repair or have no further repair.*

*In the example above, the 0.90 is not considered to be long-term success for all patients following primary repair rather success for one model cycle. This means, all initially successful first repairs will have an approximately 90% annual chance of permanent success. As long as that patient stays in the "Successful primary" it is considered permanent. Otherwise, the repair is considered to be unsuccessful – either because the repair was only temporarily successful (therefore they transition to receiving a second repair – represented by 0.0063 transition probability in this case, calculated as 10%*12.5% converted to a 1 year probability) or they receive no further repairs (until potentially receiving a knee replacement later in life).*

Table 50 (CS, page 115)

B7. Please itemise the sources of the probabilities in Table 50, including full table or page referencing.

All transition probabilities in Table 50 were taken from Table 59, page 293 of Mistry et al. 2017 (Appendix 11: Annual transition probabilities).

Excel model

B8. The columns AT ('Failed 1st TKR') and AU ('Failed 1st PKR') of the cohort flows are associated with utility values in row 19 of 0.691. The columns AV ('Successful KR') and AW ('Successful 1st KR') of the cohort flows are associated with utility values in row 19 of 0.557. This seems counter intuitive. Please clarify whether the columns have been mislabelled or incorrect utility values applied. If incorrect, please provide correct data. If correct, please outline the rationale for this.

The utility value of 0.691 associated with 'Failed 1st TKR' and 'Failed 1st PKR are correct, as these health states represent 'no further intervention following failed 1st TKR/PKR', and so the quality of patient in these states was assumed to be the same as if they required no further intervention after a successful knee replacement, as per Mistry et al. 2017. The correct value for column AW, however, should be 0.691 instead of 0.557 and so this is an error in the model and has been corrected. The updated results, based on these corrections and the corrections identified in B4/B5, are shown below. Correcting this one utility value has no impact on the results due to small numbers of patients passing through that state.

Base case results – Spherox vs. currently available technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	*£5,763*	*23.039*	*15.8736*	*..*	*..*	*..*	*..*
MF -> Spherox	*£7,156*	*23.039*	*15.9468*				*Ext. Dominated*
Spherox -> MF	*£14,182*	*23.039*	*17.9915*	*£8,419*	*0.000*	*2.1178*	*£3,975*
Spherox -> Spherox	*£15,017*	*23.039*	*18.0422*	*£835*	*0.000*	*0.0507*	*£16,466*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

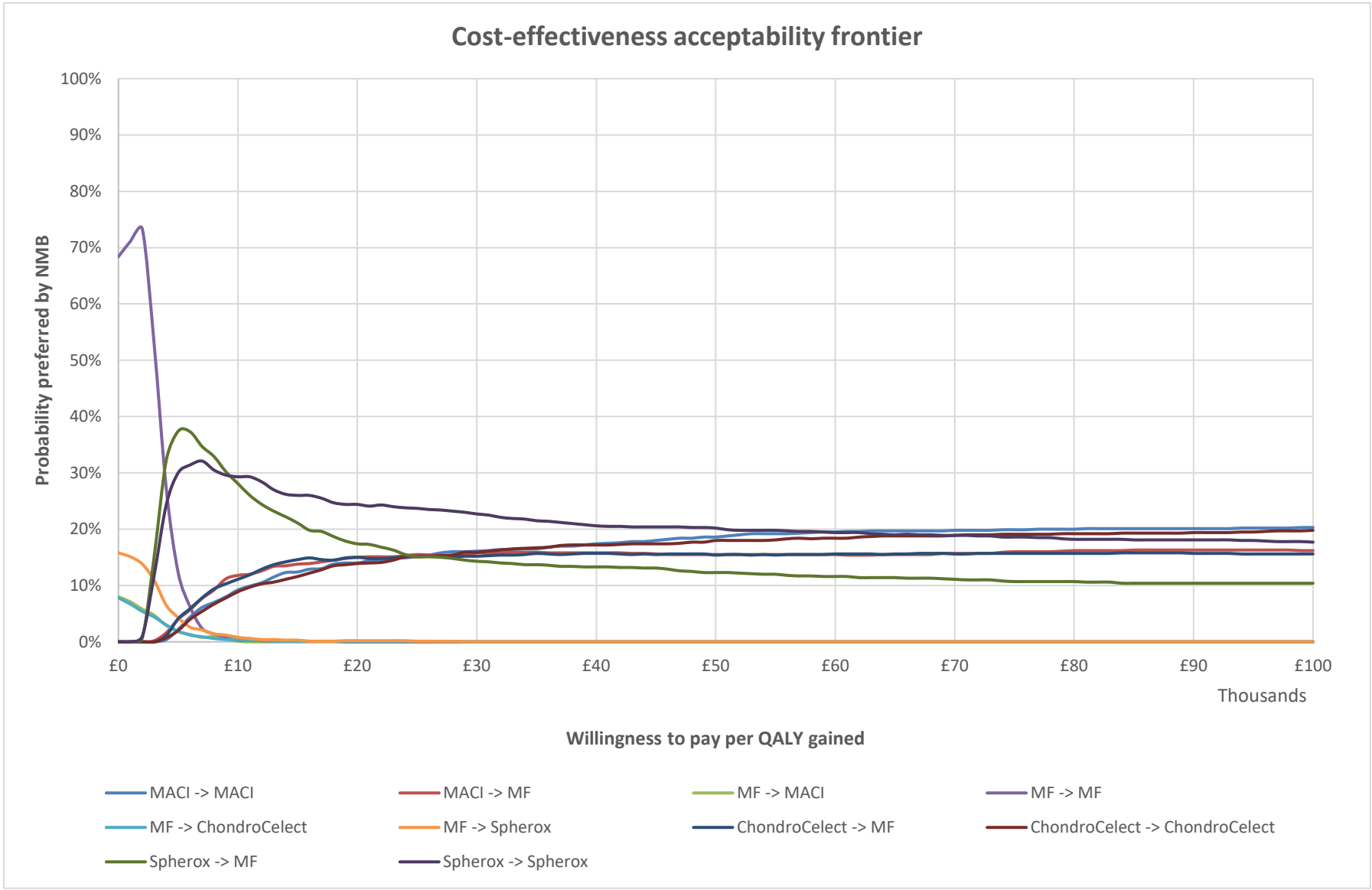
Base case results – Spherox vs. all technologies

Alternative Pathways	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
MF -> MF	*£5,763*	*23.039*	*15.8736*	*..*	*..*	*..*	*..*
MF -> Spherox	*£7,156*	*23.039*	*15.9468*				*Ext. Dominated*
MF -> ChondroCelect	*£8,168*	*23.039*	*15.9502*				*Ext. Dominated*
MF -> MACI	*£8,168*	*23.039*	*15.9504*				*Ext. Dominated*
Spherox -> MF	*£14,182*	*23.039*	*17.9915*	*£8,419*	*0.000*	*2.1178*	*£3,975*
Spherox -> Spherox	*£15,017*	*23.039*	*18.0422*	*£835*	*0.000*	*0.0507*	*£16,466*
MACI -> MF	*£20,544*	*23.039*	*18.1340*				*Ext. Dominated*
ChondroCelect -> MF	*£20,588*	*23.039*	*18.1266*				*Dominated*
MACI -> MACI	*£22,091*	*23.039*	*18.2149*		*0.000*		*Ext. Dominated*
ChondroCelect -> ChondroCelect	*£22,283*	*23.039*	*18.2205*	*£7,266*	*0.000*	*0.1783*	*£40,747*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

PSA results

Technologies	***Total costs (£)***	***Total QALYs***	***Incr costs (£)***	***Incr QALYs***	***ICER cost per QALY gained (£/QALY)***	***Preferred by NMB***
MF -> MF	*£5,609*	*15.8561*	*..*	*..*	*..*	*0.0%*
MF -> Spherox	*£6,863*	*15.9870*			*Ext. Dominated*	*0.2%*
MF -> MACI	*£7,706*	*15.9886*			*Ext. Dominated*	*0.0%*
MF -> ChondroCelect	*£7,756*	*15.9883*			*Dominated*	*0.1%*
Spherox -> MF	*£14,043*	*18.0070*	*£8,434*	*2.1509*	*£3,921*	*17.4%*
Spherox -> Spherox	*£14,721*	*18.1006*	*£678*	*0.0936*	*£7,243*	*24.4%*
MACI -> MF	*£20,416*	*18.1631*			*Ext. Dominated*	*15.0%*
ChondroCelect -> MF	*£20,419*	*18.1414*			*Dominated*	*15.0%*
MACI -> MACI	*£21,722*	*18.2551*	*£7,001*	*0.1546*	*£45,298*	*14.0%*
ChondroCelect -> ChondroCelect	*£22,006*	*18.2445*			*Dominated*	*13.9%*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval						

Figure 1 CEAF



B9. CS, section B.3.3, Table 47 (page 112). Please clarify how the value of 1.13 in the last row of the last column, labelled 'ChondroCelect (%)*' was derived. Please also indicate where this value appears in the Excel model.

This value reported in Table 47 for ChondroCelect (1.13) was a typo. The correct number should be 1.25% as per other ACIs beyond two years and this is the value currently used in the model.

Section C: Textual clarifications and additional points

C1. Document '[ID851] chondrosphere - CSR_HS13 24mo_Final Assessment - 220817 [ACIC]' (page 3) states that

[redacted]

The following economic variables were recorded but not evaluated in the phase III trial.

Hospital's perspective:

- *Length of hospital stay after biopsy*
- *Length of hospital stay after transplantation*
- *Basis for DRG grouping: ICD, OPS, comorbidities*
- *Procedural data (incision-to-closure time, staff number and costs for surgery, OP theatre costs)*
- *Transplant costs*
- *Preoperative diagnostic measures*
- *Length of wound healing*

Health insurance's perspective:

- *Other treatment-specific costs (e.g. outpatient preoperative diagnostics)*
- *Days off work (beyond 42 days)*
- *Days and costs of inpatient follow-up rehabilitation ("Anschlussheilbehandlung", AHB, if applicable)*
- *Outpatient disease-related or procedure-related drugs*
- *Outpatient disease-related or procedure-related physician consultations (e.g. due to post-procedural complications)*
- *Procedures initiated by outpatient physician (e.g. MRI, CT, X-ray, arthroscopy)*

Employer's perspective:

- *Days off work (up to 42 days)*

Pension fund's perspective:

- *Type of rehabilitation (in-/outpatient, if applicable)*
- *Length of rehabilitation*
- *Costs of rehabilitation*

C2. Document '2017appendix_16.1.1' (pages 231-232) states

[redacted]

When there was inability of transplantation in the past, most instances occurred due to insufficient cell quality to generate sufficient spheroids. Specifically, cell culture could not be commenced due to:

- *Positive serology/infectious status following the biopsy sample (e.g. infection with the hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV I/II viruses).*
- *Insufficient biopsy quality.*

Inability of transplantation may also be due to other reasons besides insufficient cell quality to generate cell culture. For instance, if the transplantation was cancelled by the patient or by the surgeon, e.g. because the patient was ill on surgery day.

C3. CS, section B.1.3 (page 19). The submission states that "*Spherox treatment application is less invasive than other ACIs, resulting in lower healthcare resource utilization and providing similar or greater health benefits at a lower cost than other ACIs or ACI technologies.*"

- Please clarify in what way the Spherox application is less invasive, for example, undertaken via mini-arthrotomy or arthroscopy.
- Please provide the average time taken for each of these procedures, that is arthrotomy, arthroscopy etc.
- Please clarify whether the time taken in these procedures affect spheroid viability.

The Consultant Orthopaedic Surgeon has the option to implant Spherox via Arthroscopy. Spherox does not require any additional fixation (fibrin glue or surgical sutures) nor any additional matrix/scaffold as required by 3rd generation ACI technologies (MACI/ChondroCelect) and Traditional ACI.

The difference in actual theatre operating time is down to the experience of the operating surgeon but as a general guide they are as follows:

- *Arthroscopy for implantation of Spherox – 30/40 minutes*
- *Mini-Arthrotomy for other ACI– 60 minutes*
- *Traditional ACI with mini-arthrotomy – 60 minutes*

There is no effect on Spheroid viability whether it is implanted via arthroscopy or mini-arthrotomy as Spherox is not removed from its protective packaging until preparation has been achieved e.g. debridement of lesion.

Single technology appraisal

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

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have reviewed the responses to the clarification questions received on Friday 22nd September 2017 from Co.don AG. There are several outstanding queries (A8i, A9i, A10i, A12i, B2i, B3i and B10) highlighted in red text below the company's blue italicised responses.

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the follow up clarification questions by **5pm** on **6 October**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

The Company has provided written responses to the clarification questions in blue italicized text directly below each question. Additional documents (e.g. spreadsheets, publications) referenced in the responses were submitted along with this response document to NICE.

Section A: Clarification on effectiveness data

Phase 2 trial

Inadequate spheroid production

A8. CS, section B2.4.2 (page 47). The submission states that "*… predominantly too low doses due to inadequate cell proliferation in culture*". Please clarify what happens to patients for whom there are inadequate spheroids to cover the defect.

The phase II trial was designed as a dose confirmation study with three doses (low: 3-7 spheroids/cm², medium: 10-30 spheroids/cm² and high: 40-70 spheroids/cm²). The 48 months follow-up results revealed that no dose response was observed. The dose of the product Spherox is defined as 10-70 spheroids/cm² implantation suspension. In the phase II trial, some samples from the high dose group showed a lower cell proliferation in culture and thus a product dose fulfilling the medium dose was transplanted. Thus some patients received lower doses than intended due to their randomisation group, but always a sufficient spheroid dose. The transplanted spheroid dose was always within the specification of 10-70 spheroids/cm² and was therefore always adequate to cover the defect.

A8i. Follow up to question A8. Beyond the trial data, please clarify what would happen to patients for whom there are inadequate spheroids to cover the defect.

Subgroup analysis

A9. Appendix E, Subgroup analysis for phase 2 trial (pages 36-39). There is evidence to suggest that the effectiveness of previous generations of ACI is reduced in people with a history of microfracture. Please clarify whether there are data available on treatment success or failure for the following subgroups:

- Duration of injury
- Previous repair attempts involving the subchondral bone

If yes, please provide the data.

Minas et al. 2009 (publication submitted with this ERG response) evaluated the failure rates of ACI conducted after previous treatment with marrow stimulation techniques and the results demonstrate that marrow stimulation techniques, like MF, have a strong negative effect on subsequent cartilage repair with ACI and therefore should be used judiciously in larger cartilage defects that could require future treatment with ACI.

Furthermore the Phase III trial assessed the duration of knee symptoms for both treatment groups Spherox and MF. However, in this trial, previous treatment with ACI in the affected knee was an exclusion criteria. The cut-off value between the long- and short-duration subgroups was 1 year. The KOOS results (mean differences with respective 95% confidence intervals) for the MF group at 24 months after treatment revealed better KOOS values (mean ± SD, [redacted]) for patients with a documented symptom duration of < 1 year compared the symptoms durations > 1 year (mean ± SD, [redacted]). Corresponding results for the Spherox group at Visit 6, 24 months after treatment, were:

- *< 1 year: mean ± SD, [redacted]*
- *>1 year: mean ± SD, [redacted]*

A9i. Follow up to question A9. These data refer to the Phase 3 trial (COWISI), please provide data for the **Phase 2** trial.

Network meta-analysis

Dataset

A10. PRIORITY QUESTION. CS, section B.2.9 (pages 77-79). Please provide the datasets used for the 2 outcomes (number of responders and failure rates) derived from the 3 randomised controlled trials included in the network meta-analysis. Please provide this information in an Excel spreadsheet.

The Excel spreadsheet (A10_NMA_DATA) with this dataset was submitted with this response document.

A10i. Follow up to question A10. Clarification response NMA data "[ID851] chondrosphere - 8. A10_NMA_DATA - 220917 [ACIC]". Please clarify the headings t[,1] t[,2] na[] rp[] np[].

comparison 1 vs 2	t[,1]	t[,2]	na[]	rp[]	np[]
MF vs Spherox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MF vs MACI	1	3	2	49	72
MF vs Chondrocelect	1	4	2	31	50

Results

A12. PRIORITY QUESTION. CS, section B.2.9.1, figures 12 and 13 (pages 78 and 79).

- **Figure 12 Response rates (CS, page 78).**
    - Table 47 (CS, page 112) provides probabilities of response (or risks) of [redacted] for Spherox (chondrosphere) and 86.57% for ChondroCelect. This results in a relative risk of 1.068 (86.57/[redacted]) which differs from the reported value of 1.209 in Figure 12. Please explain this difference.

The number reported in Table 47 for ChondroCelect was calculated by applying the relative risk (RR) from the NMA, which for ChondroCelect compared to Spherox was 1.209, to the rate for Spherox and converted to a probability using the following approach:

1. *Spherox rate: -(LN(1-[redacted]))=1.66*
2. *ChondroCelect rate: 1.66*1.209=2.01*
3. *ChondroCelect probability: 1-EXP(-2.01)=86.57%*

A12i. Follow up to question A12. Please explain why there is a difference between the implied relative risk of 1.068 (86.57/[redacted]) based on figures from Table 47 compared to the reported value of 1.209 used in Figure 12.

<u>Section B: Clarification on cost-effectiveness data</u>

Technology

Costs

B2. CS, section B2.4.2 (page 47). As stated in the submission, there are situations when there is no or only inadequate cell growth. Please clarify the costs to the NHS in these circumstances, for example harvesting arthroscopy.

For any knee cartilage lesion, an arthroscopy is performed to assess the size of the lesion. If treatment with Spherox is needed, harvesting of the cells is then performed during this procedure. In situations where there may be no or inadequate cell growth to facilitate cultivation after harvesting, due to the quality or quantity of the cells harvested, a repeat arthroscopy would be needed to harvest additional cells.

There would be no additional Spherox related costs incurred to the NHS in these extremely rare instances. The NHS is only invoiced once delivery of Spherox is made.

B2i. Follow up to question B2. Please qualify 'extremely rare', for example, less than 1%?

Expired products

B3. PRIORITY QUESTION. Appendix C, Summary of product characteristics (page 8). The SmPC states that the shelf life for Spherox is 72 hours. Please clarify what happens if implantation has to be deferred for weeks or months. For example, are there cases when a second biopsy and culture are necessary?

If there was a deviation beyond the implantation time-frame (after acceptance of the delivery of the cells for implantation by the hospital) that went beyond the 72 hours shelf life** of the cells for implantation, then the implantation could not take place and these cells discarded. Therefore, a new sample (biopsy) would need to be harvested and the culture process repeated.*

** The time-frame to cells being available for implantation is a maximum period of 55 days from day of harvesting. There is no deferment beyond the 55 days.*

*** The 72 hour shelf life is the period the cells (spheroids) are viable for implantation once delivered to the hospital for implantation.*

B3i. Follow up to question B3. Postponement of admissions is not uncommon, for example, if patients are unwell. Spherox may have been requested before the procedure has to be postponed. Please provide an account of the experience from Germany, including how often a second biopsy is necessary.

Model

Follow up question B10. PRIORITY QUESTION. Clarification response Economic model "[ID851] chondrosphere - 10. Spherox_ID851_EconomicModel_22SEPT2017 - 220917 [ACIC]". In the revised economic model submitted with the clarification response, please document **all** changes, together with full cell referencing.

Single technology appraisal

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

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have reviewed the responses to the clarification questions received on Friday 22nd September 2017 from Co.don AG. There are several outstanding queries (A8i, A9i, A10i, A12i, B2i, B3i and B10) highlighted in red text below the company's blue italicised responses.

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the follow up clarification questions by **5pm** on **6 October**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

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If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

The Company has provided written responses to the clarification questions in blue italicized text directly below each question. Additional documents (e.g. spreadsheets, publications) referenced in the responses were submitted along with this response document to NICE.

Section A: Clarification on effectiveness data

Phase 2 trial

Inadequate spheroid production

A8i. Follow up to question A8. Beyond the trial data, please clarify what would happen to patients for whom there are inadequate spheroids to cover the defect.

For study purposes, and beyond the trials, each pre-filled syringe or applicator contains a specific number of spheroids according to the defect size (10-70 spheroids/cm^2) to be treated. Thus the specification of 10-70 spheroids/cm² ensures that the implanted spheroids will be able to cover the defect.

In cases of inadequate spheroid manufacturing (i.e. inadequate cell proliferation produces a spheroid dose <10 spheroids/cm^2), the transplantation will be cancelled. From experience in Germany, in 2.4% of the incoming biopsies the manufacturing was inadequate to produce spheroids.

Subgroup analysis

A9i. Follow up to question A9. These data refer to the Phase 3 trial (COWISI), please provide data for the **Phase 2** trial.

Similar to the Phase III trial, in the Phase II trial previous treatment with ACI in the affected knee and MF performed less than 1 year before screening in the affected knee was an exclusion criteria.

The "duration analysis" subgroup results are shown below. Due to the study design of this Phase II dose confirmation study, the results are based on Spherox data only. For a total of [redacted] treated patients, the 4 year follow-up analysis yielded the following results:

- *< 1 year: n=[redacted]; mean ± SD, [redacted]*
- *>1 year: n=[redacted]; mean ± SD, [redacted]*

Network meta-analysis

Dataset

A10i. Follow up to question A10. Clarification response NMA data "[ID851] chondrosphere - 8. A10_NMA_DATA - 220917 [ACIC]". Please clarify the headings t[,1] t[,2] na[] rp[] np[].

comparison 1 vs 2	t[,1]	t[,2]	na[]	rp[]	np[]
MF vs Spherox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MF vs MACI	1	3	2	49	72
MF vs Chondrocelect	1	4	2	31	50

The headings refer to the following:

- *t [,1] refers to the treatment of the comparator arm in each of the included studies, i.e. MF (labelled as "1" according to the Treatment Index included in the spreadsheet).*
- *t [,2] refers to the treatment of the intervention arm in each of the included studies; according to the Treatment Index, Spherox is assigned the treatment number "2", MACI is assigned the treatment number "3", and ChondroCelect is assigned the treatment number "4".*
- *na [ ] refers to the number of arms in each of the included studies*
- *rp [ ] refers to the number of responders or number of failures in the reference treatment arm (i.e. MF) of each trial (the same as r [,1] in the spreadsheet).*
- *np [ ] is the total number of patients in the reference treatment (i.e. MF) arm of each trial (the same as n [,1] in the spreadsheet).*

Results

A12i. Follow up to question A12. Please explain why there is a difference between the implied relative risk of 1.068 (86.57/[redacted]) based on figures from Table 47 compared to the reported value of [redacted] used in Figure 12.

The original approach was an incorrect application of the NMA data. Please see the updated values below incprorated in the model:

Intervention	*Response rate*	*Source*
Microfracture	*78.44%*	*NMA*
Spherox	*79.50%*	*NMA + OR from trial*
MACI	*92.28%*	*NMA + OR from trial*
ChondroCelect	*91.59%*	*NMA + OR from trial*

The updated incremental base case results are shown below:

Alternative	Cost	QALYs	Inc Cost	Inc QALYs	Cost per QALY gained
MF -> MF	£5,762	15.8778	..	..	..
MF -> Spherox	£7,152	15.9439			Ext. Dominated
MF -> ChondroCelect	£8,162	15.9509			Ext. Dominated
MF -> MACI	£8,162	15.9513			Ext. Dominated
Spherox -> MF	£14,174	17.9546	£8,412	2.0767	£4,051
Spherox -> Spherox	£14,993	17.9997	£819	0.0452	£18,137
MACI -> MF	£20,595	18.2616			Ext. Dominated
ChondroCelect -> MF	£20,615	18.2440			Dominated
MACI -> MACI	£22,312	18.3949	£7,319	0.3951	£18,523
ChondroCelect -> ChondroCelect	£22,400	18.3860			Dominated

Section B: Clarification on cost-effectiveness data

Technology

Costs

B2i. Follow up to question B2. Please quality 'extremely rare', for example, less than 1%?

In 2.4% of the incoming biopsies the manufacturing was inadequate to produce spheroids.

Expired products

B3i. Follow up to question B3. Postponement of admissions is not uncommon, for example, if patients are unwell. Spherox may have been requested before the procedure has to be postponed. Please provide an account of the experience from Germany, including how often a second biopsy is necessary.

The experience in Germany is that less than 1% of the incoming biopsies required a second biopsy.

Model

Follow up question B10. PRIORITY QUESTION. Clarification response Economic model "[ID851] chondrosphere - 10. Spherox_ID851_EconomicModel_22SEPT2017 - 220917 [ACIC]". In the revised economic model submitted with the clarification response, please document **all** changes, together with full cell referencing.

In addition to the changes tabulated below, all confidentiality marking was removed.

Tab	*Cell Reference*	*Original Value*	*Updated Value*	*Reason for change*
Clinical Inputs	*F25*	*79.75%*	*17.75%*	*Reinterpretation of data*
Clinical Inputs	*F27*	*81.00%*	*19.00%*	*Reinterpretation of data*
Clinical Inputs	*F31*	*78.26%*	*16.59%*	*Reinterpretation of data*
Clinical Inputs	*F33*	*81.00%*	*18.30%*	*Reinterpretation of data*
Clinical Inputs	*F37*	*78.26%*	*16.59%*	*Reinterpretation of data*
Clinical Inputs	*F39*	*79.98%*	*18.30%*	*Reinterpretation of data*
Clinical Inputs	*F43*	*79.75%*	*17.75%*	*Reinterpretation of data*
Clinical Inputs	*F45*	*79.98%*	*19.00%*	*Reinterpretation of data*
Clinical Inputs	*F49*	*85.63%*	*11.87%*	*Reinterpretation of data*
Clinical Inputs	*F51*	*86.88%*	*13.12%*	*Reinterpretation of data*

Clinical Inputs	*F55*	*85.63%*	*11.87%*	*Reinterpretation of data*
Clinical Inputs	*F57*	*79.98%*	*13.12%*	*Reinterpretation of data*
Clinical Inputs	*F61*	*78.26%*	*16.59%*	*Reinterpretation of data*
Clinical Inputs	*F63*	*86.88%*	*18.30%*	*Reinterpretation of data*
Clinical Inputs	*F67*	*85.32%*	*11.16%*	*Reinterpretation of data*
Clinical Inputs	*F69*	*86.57%*	*12.41%*	*Reinterpretation of data*
Clinical Inputs	*F73*	*85.32%*	*11.16%*	*Reinterpretation of data*
Clinical Inputs	*F75*	*79.98%*	*12.41%*	*Reinterpretation of data*
Clinical Inputs	*F79*	*78.26%*	*16.59%*	*Reinterpretation of data*
Clinical Inputs	*F81*	*86.57%*	*18.30%*	*Reinterpretation of data*
MF -> MF	*AW19*	*0.557*	*0.691*	*Cell reference correction*
Spherox -> MF	*AW19*	*0.557*	*0.691*	*Cell reference correction*
Spherox -> Spherox	*AW19*	*0.557*	*0.691*	*Cell reference correction*
MACI -> MF	*AW19*	*0.557*	*0.691*	*Cell reference correction*
MACI -> MACI	*AW19*	*0.557*	*0.691*	*Cell reference correction*
ChondroCelect -> MF	*AW19*	*0.557*	*0.691*	*Cell reference correction*
ChondroCelect -> ChondroCelect	*AW19*	*0.557*	*0.691*	*Cell reference correction*
MF -> Spherox	*AW19*	*0.557*	*0.691*	*Cell reference correction*
MF -> MACI	*AW19*	*0.557*	*0.691*	*Cell reference correction*
MF -> ChondroCelect	*AW19*	*0.557*	*0.691*	*Cell reference correction*

Single technology appraisal

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

Dear Graeme,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have reviewed the responses to the clarification follow up questions received on Friday 6th October from Co.don AG. There is one outstanding query (A12ii) highlighted in red text below the company's blue italicised responses.

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Section A: Clarification on effectiveness data

Network meta-analysis

Results

A12i. Follow up to question A12. Please explain why there is a difference between the implied relative risk of 1.068 (86.57/[redacted]) based on figures from Table 47 compared to the reported value of [redacted] used in Figure 12.

The original approach was an incorrect application of the NMA data. Please see the updated values below incprorated in the model:

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A12ii. Follow up to question A12i. For Spherox, MACI and ChondroCelect, the source of response rate is stated to be “NMA + OR from trial”. Please clarify how both the “NMA + OR from trial” were used to derive the response rate for these 3 groups. For all 3 groups, please provide full details of the point estimates derived from the NMA and the OR from the trial, specifying which trial is being referenced.

Single technology appraisal

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

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Section A: Clarification on effectiveness data

Network meta-analysis

Results

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Company response:

In a first step, odds ratios (OR) were calculated using respective trial data on the proportion of responders for each intervention (Spherox, MACI, and ChondroCelect) relative to the common comparator (MF) in COWISI, SUMMIT and TIG/ACT trials:

$$OR = (P1/ 1- P1)/ (P2/1- P2)$$

Where P1 is the probability of response for each intervention (Spherox, MACI, ChondroCelect) and P2 is the probability of response for the comparator (MF).

Trial input data and calculated ORs (OR_{TX}) are summarised in the table below.

Trial	***Treatments***	***Responders***	***OR***
COWISI	*Spherox*	*[redacted]%*	*1.066*
	MF	*[redacted]%*	
SUMMIT	*MACI*	*88%*	*3.286*
	MF	*68%*	
TIG/ACT	*ChondroCelect*	*83%*	*2.993*
	MF	*62%*	

In a second step, the 'reference' response rate for MF was calculated by multiplying the relative risk from the NMA for MF vs. Spherox, which was 0.9684 (listed in Figure 12 in the main NICE submission document), by the responder rate for Spherox from the COWISI trial ([redacted]%), i.e. 0.9684[redacted]= 0.7844. The odds of response for MF (O_{MF}) therefore are given as 0.7844/(1-0.7844) = 3.638.*

To derive treatment-specific response rates (r_{TX}), the calculated ORs (OR_{TX}) were applied to the odds of response for MF (O_{MF}) as follows:

$$r_{TX} = OR_{Tx}*O_{MF}/(1+OR_{Tx}*O_{MF})$$

The resulting response rates are given in the response to A12i but as an example, the r_{TX} for Spherox would be calculated as follows:

$$r_{Sphx}=1.066*3.638/(1+(1.066*3.638))$$

$$r_{Sphx}=79.50\%$$

Additional scenarios were tested, using the same methodology as described above with the following exceptions:

1. *Applying ORs derived from the NMA instead of trial-derived ORs (i.e. Spherox vs. MF OR = 1.118; MACI vs. MF OR = 3.374; ChondroCelect vs. MF OR = 3.086)*
2. *The same as (1) above, and also determining the rate of response for MF by applying the OR rather than the RR from the NMA (i.e. MF vs. Spherox OR = 0.8945 instead of RR = 0.9684)*

Results of these additional scenarios are given below:

Scenario 1:

Full deterministic results

Alternative	Cost	QALYs	Inc Cost	Inc QALYs	Cost per QALY gained
MF -> MF	£5,762	15.8778	..	..	..
MF -> Spherox	£7,152	15.9443			Ext. Dominated
MF -> ChondroCelect	£8,163	15.9510			Ext. Dominated
MF -> MACI	£8,163	15.9514			Ext. Dominated
Spherox -> MF	£14,178	17.9734	£8,416	2.0955	£4,016
Spherox -> Spherox	£15,005	18.0214	£827	0.0480	£17,233
MACI -> MF	£20,596	18.2659			Ext. Dominated
ChondroCelect -> MF	£20,616	18.2494			Dominated
MACI -> MACI	£22,316	18.4013	£7,311	0.3799	£19,243
ChondroCelect -> ChondroCelect	£22,405	18.3941			Dominated

Scenario 2:

Full deterministic results

Alternative	Cost	QALYs	Inc Cost	Inc QALYs	Cost per QALY gained
MF -> MF	£5,767	15.8764	..	..	..
MF -> Spherox	£7,168	15.9470			Ext. Dominated
MF -> ChondroCelect	£8,187	15.9536			Ext. Dominated
MF -> MACI	£8,187	15.9540			Ext. Dominated
Spherox -> MF	£14,182	17.9914	£8,415	2.1150	£3,979
Spherox -> Spherox	£15,017	18.0422	£835	0.0508	£16,438
MACI -> MF	£20,598	18.2734			Ext. Dominated
ChondroCelect -> MF	£20,618	18.2574			Dominated
MACI -> MACI	£22,324	18.4124	£7,307	0.3702	£19,738
ChondroCelect -> ChondroCelect	£22,413	18.4063			Dominated

Overall, the cost effectiveness results were found to remain consistent across the range of scenarios tested, using either trial- or NMA-derived inputs.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Philipp Niemeyer

Name of your organisation OCM Clinic Munich, Germany & Department of Orthopedic Surgery and Traumatology, Freiburg University Hospital, Germany

Are you (tick all that apply):

✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?

✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Currently, in the UK, patients with symptomatic articular cartilage defects in the knee will first be offered best supportive care (weight loss, physiotherapy, corticosteroid injections, and pain medication) before surgical interventions. If symptoms persist, the patient will be considered for reparative/restorative procedures which may include knee lavage (with or without debridement, the removal of damaged cartilage), microfracture, mosaicplasty, and autologous chondrocyte implantation (ACI). I believe ACI is the preferred choice in UK clinical practice, however, due to access issues microfracture is the most common procedure performed. If symptoms persist after MF or ACI, other interventions will be considered, including mosaicplasty or ACI. MF would not be preferred as a second intervention if MF was previously performed. Knee replacement (total and partial) are only considered as the last treatment option in UK clinical practice if osteoarthritis develops.

I am not aware of a variation in clinical practice in this area. Professional opinion is consistent on the pathway of care in Germany.

Microfracture is limited in that it produces fibrocartilage, which is less durable than normal hyaline cartilage. The most important limitation of Microfracture ~~is also less suitable for large lesions~~is defect size, and so there is an unmet need for a new therapy for these patients. ACIs were introduced as an alternative treatment option and the aim was to produce hyaline cartilage. Earlier generations of ACI administered the chondrocytes under a periosteal flap or biodegradable membrane, which was problematic as additional surgical procedures were often required. The current generation of ACIs (MACI and ChondroCelect) are not currently licensed nor available in the UK and so these patients do not have an alternative therapeutic option.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Spherox is an effective option in all patients with lesion sizes 1-10cm^2 but is likely to work better than microfracture in patients with larger lesions.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The summary of product characteristics states that Spherox "…must be administered by an appropriately qualified physician and in a medical facility. In Germany, Spherox is used in specialist centres.

The following documents are required prior to Tissue Procurement for Spherox in UK:
1. Proof of a valid Human Tissue Authority (HTA) licence;
2. Signed Tripartite Agreement Spherox;
3. Completed Training of physicians and HCP;
4. Training Certificate;
5. Audit Questionnaire (Audit conducted by CODON)

Training would be required on the implantation of Spherox but all other procedures involved would be familiar to an orthopaedic surgeon.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not applicable

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

According to the German Society of Orthopaedics and Traumatology (DGOU), ACI is indicated for symptomatic cartilage defects starting from defect sizes of more than 3-4 cm^2; in the case of young patients or those active in sports at 2.5 cm^2. Also a consensus of 104 UK clinical experts considered ACI as the only effective option for treating defects greater than 2 cm2 when symptoms persist following non-surgical management (Biant et al. 2015).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

In the UK, the introduction of Spherox would give patients an alternative treatment option to microfracture, particularly for those with larger lesion sizes, and given that other ACIs are not accessible. Whilst there are some advantages to the use of Spherox over other ACIs, such as involving arthroscopy only, self-adherence of the chondrocytes and being 100% autologous, the mechanism of action and process is relatively similar. Compared with microfracture, there are a number of differences in the way Spherox is likely to be used.

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Single Technology Appraisal (STA)

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Not applicable

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I believe that all relevant clinical outcomes were included in the Spherox trials. The study design was developed in 2008 and was based on comparable studies by Saris. Both trials were planned with a 5 year follow up period to cover the long term outcome. In my view both trials are generalizable to the UK clinical practice setting.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Both clinical trials were developed to document all adverse events, from treatment related to non-treatment related, like headache. Therefore, a wide range of adverse events was measured during the trials and no "new" adverse effect was detected during this routine data collection.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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Single Technology Appraisal (STA)

None

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Data from the German register http://www.knorpelregister-dgou.de/start/ could be used.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As there is currently no EMA licenced ACI available to patients who would benefit, NICE guidance could allow patient access to Spherox (which fully EMA ATMP licensed for ACI) to those patients who would benefit.

The following documents are required prior to Tissue Procurement for Spherox in UK:
1. Proof of a valid Human Tissue Authority (HTA) licence;
2. Signed Tripartite Agreement Spherox;

3. Completed Training of physicians and HCP;
4. Training Certificate;
5. Audit Questionnaire (Audit conducted by CODON)

Training would be required on the implantation of Spherox but all other procedures involved would be familiar to an orthopaedic surgeon.

Autologous chondrocyte implantation with Spherox for treating articular cartilage defects in the knee. (NICE ID 851)

Warwick Evidence ERG report October 19th 2017

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Contribution of authors;
Norman Waugh and Xavier Armoiry wrote the clinical effectiveness section, assisted by Jeremy Rodrigues. Norman Waugh co-ordinated the project and wrote Chapters 1 and 5. Ewen Cummins wrote the cost-effectiveness section, assisted by Rhona Johnston and Hema Mistry. Pamela Royle conducted literature searches. Andrew Metcalfe provided expert advice and commented on drafts. Norman Waugh and Pamela Royle edited the final document.
Text highlighted in yellow is academic in confidence.

Table of Contents

List of Tables

Table of Figures

LIST OF ABBREVIATIONS

ACI	Autologous chondrocyte implantation
AE	Adverse event
AEs	Adverse events
ANCOVA	Analysis of covariance
BMI	Body mass index
BSC	Best supportive care
CC	ChondroCelect
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EPAR	European public assessment report
GAGs	Glycosaminoglycans
ICER	Incremental cost-effectiveness ratio
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
ITT	Intention-to-treat
K-L	Kellgren-Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
KR	Knee replacement
MACI	Matrix-Applied Characterized Autologous Cultured Chondrocytes
MF	Microfracture
MOCART	Magnetic resonance observation of cartilage repair tissue
MRI	Magnetic resonance imaging

NFR	No further repair
NMA	Network meta-analysis
NMB	Net monetary benefit
OA	Osteoarthritis
OCD	Osteochondritis dissecans
OP	Outpatient
PKR	Partial knee replacement
PP	Per protocol
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized clinical trial
ROB	Risk of Bias
RR	Relative risk
SD	Standard Deviation
SE	Standard Error
SPHX	Spherox
TKR	Total knee replacement
WTP	Willingness-to-pay

1 Summary

1.1 Critique of the decision problem in the Co-Don submission

The Co-Don summary of the decision problem is similar to the NICE scope, except that Co-Don consider that some of the comparators were inappropriate, including osteotomy and mosaicplasty. The ERG agrees with the Co-Don position. Mosaicplasty is little used in the UK and we think it would be used only for small lesions.

The FAD from the recent MTA of autologous chondrocyte implantation (ACI) recommended that it should be used, subject to some restrictions, one of which was size of the articular cartilage (chondral) defect. This means that the NICE scope issued for this STA is out of date, and microfracture is no longer a comparator for defects over 2 cm^2. The key comparators are now other forms of ACI, though there are problems with the availability of these, as reported later. So the decision problem as defined by Co-Don is also out of date – the timing was unfortunate.

The outcomes in the Co-Don decision problem are as in the NICE scope.

1.2 Summary of the clinical effectiveness evidence submitted by Co-Don

Trials

The Co-Don submission presents the results from two RCTs (one phase II and one phase III).

The phase II RCT was conducted prior to the phase III and aimed to identify the optimal strength of Spherox by comparing three arms with different doses. This study included people with large defects (4-10cm^2). The KOOS score improved from a baseline mean of [redacted], median [redacted], to a mean of [redacted], median [redacted] at four years. So the key result is that improvements seen at 24 months are sustained.

The phase III study, called COWISI, was the pivotal trial to support the approval of Spherox.

COWISI is a prospective, randomised, open label, multicentre phase III clinical trial that compared Spherox to microfracture (MF) in 102 patients with defect sizes between 1 and 4cm^2. The outcomes in the trial match the NICE scope. The primary outcome was the change of overall KOOS from day 0 to assessment at 24 months after treatment completion. The KOOS score, together with other outcomes

such as MOCART (MRI score) will be evaluated with longer term follow-up durations (36, 48, 60 months) that are not yet available.

COWISI was a good quality trial though blinding of intervention was impractical because the Spherox group had two procedures. The sample size was calculated to show non-inferiority of Spherox against MF whereas other trials of ACI (SUMMIT, TIG/ACT, and ACTIVE) were designed to show if ACI was superior to MF.

The KOOS scores improved from baseline to 24 months with both Spherox (improvement of [redacted]) and MF ([redacted]). The repeated-measures ANCOVA testing for non-inferiority of Spherox against MF showed a [redacted] difference with a lower bound [redacted].

Safety was assessed through the incidence of adverse events (AE) that were probably or possibly related to treatments. In the phase II trial only [redacted] of 73 patients treated had severe adverse events, [redacted].

Network meta-analysis:

The Co-Don submission presented indirect evidence for comparisons of Spherox with two other forms of ACI, ChondroCelect and Vericel MACI, via a network meta-analysis (NMA). The network included three RCTs and used microfracture as a common comparator. Two outcomes were assessed, responders and failures. The studies varied in how response was reported, with response was defined in two trials as a gain of 10 or more points in the overall KOOS scale, and in the third as gains in several KOOS subscales. Failure was a need for revision surgery. [redacted]. The proportions of [redacted] ChondroCelect. [redacted]. At clarification stage, the Company provided the dataset used to run the NMA on the two outcomes. Using a frequentist framework, the ERG was able to replicate the findings of the Company's NMA on responders but found different results for the NMA on failure. However, this was not considered as a major issue given that failure inputs in the cost-effectiveness model used data from RCTs and not those from the NMA.

1.3 Summary of the ERG critique of the clinical effectiveness evidence submitted by Co-Don

COWISI was a good quality trial though blinding of intervention was impossible, and protocol deviations were seen in [redacted]. The largest number of deviations was because of failure to attend visits, with taking of prohibited pain medications next (mainly in the MF group). The main problem with the trial at present is that results are only available to 24 months. Longer-term follow-up is planned, to five years.

Although the Phase II dosage study was of reasonable quality, apart from the [redacted] drop-out rates due to protocol violations, it is of limited interest because it did not include any comparator listed in the NICE scope and therefore was not used to inform the cost-effectiveness model.

The ERG has identified several methodological flaws in the NMA, in particular focusing on the assumptions of homogeneity and similarity.

- The transitivity assumption does not hold, since the distribution of population characteristics that are effect modifiers differ across the treatment comparisons of the network. Three such treatment effect modifiers in the Co-Don NMA are the baseline KOOS score, the lesion size at baseline, and previous repair attempts. The uneven distribution of these effect modifiers across the network comparisons violates the transitivity assumption.
- The networks compared interventions for two outcomes, namely the proportion of responders and failure rate. However there was some variation in the definition of both outcomes which means that the outcomes were not assessed consistently across studies. Furthermore, failure rates were not evaluated over the same time periods across studies. Outcomes using time-varying events should be assessed consistently to enable a valid comparison.

The ERG doubts whether it was appropriate to do an NMA, and considers the validity of the estimate for the indirect comparisons to be very questionable.

Given the paucity of RCT data, the ERG looked to see if anything could be gleaned from case series. However these are mainly small, three are just pilot studies, two are available only as conference abstracts, and others have duration of only for around a year. Without control groups, their value is limited. They do report before and after improvements, showing that Spherox is clinically effective, and also that Spherox can be implanted arthroscopically.

1.4 Summary of cost effectiveness evidence submitted by Co-Don

The company model structure is meant to mirror that of the model of the ACI MTA. It is a markov model with an annual cycle and a lifetime horizon. All patients receive the 1st repair of the sequence during the 1st cycle of the model. These patients can move into one of three health states.

- Success
- No further repair (NFR)
- 2nd repair, if necessary

Subsequent to the 1st cycle those who were a success either remain a success or move to 2nd repair. All those in NFR remain in NFR.

The patients who receive the 2nd repair of the sequence can move into one of two health states.

- Success
- No further repair (NFR)

Those who were a success either remain a success or move to NFR. All those in NFR remain in NFR. No further repairs are possible after a 2nd repair.

From age 55, a common probability of patients receiving knee replacements is applied.

Four main sets of comparators are included.

- A 1st microfracture repair with the possibility of a 2nd microfracture repair
- A 1st microfracture repair with the possibility of a 2nd ACI repair
- A 1st ACI repair with the possibility of a 2nd microfracture repair
- A 1st ACI repair with the possibility of a 2nd ACI repair

When a 1st ACI repair is followed by a 2nd ACI repair the same ACI is given. ERG expert opinion suggests that this it reasonable because centres are likely to specialise in a single type of repair.

The company derives the clinical effectiveness estimates from its NMA on success rates and its NMA on failure rates. Quality of life values are aligned with those of the ACI MTA. Unit costs are largely aligned with those of the 1st AG model of the ACI MTA. Cell costs are £10,000 for Spherox and £16,000 for MACI and ChondroCelect.

Following clarifications the company has revised some of its clinical effectiveness estimates. The company revised cost effectiveness estimates are that the cost effectiveness of Spherox relative to microfracture is around £4k per QALY and the cost effectiveness of MACI compared to Spherox is around £18k per QALY.

There are no sensitivity analyses around the revised company estimates. The original modelling was most sensitive to the assumption that all microfracture repair successes fail at year 5.

1.5 Summary of the ERG critique of the cost effectiveness evidence submitted by Co-Don

The company model differs from that of the model of the ACI MTA in one crucial respect. 1st repair successes cannot lose response and move into the no further repair health state. This is likely to bias the analysis in favour of the ACIs. It may also further bias the analysis in favour of MACI and ChondroCelect if their loss of response is similar to that of Spherox, because their initial success proportion is a bit higher.

The response estimates for 2nd repairs are only applied once within the modelling and as a consequence the company method used to derive these is incorrect.

The company accepts that the probabilities of 2nd repair successes losing success and moving to no further repair are incorrect. It suggests revising these to be based upon the annualised 1st repair non-response probabilities at 2 years. These estimates are applied every year of the model, do not really relate to a loss of response, and are probably too high.

The company clinical effectiveness estimates are incorrect and biased in favour of Spherox.

The company quality of life estimates are aligned with those of the ACI MTA.

The company does not apply the preferred set of unit costs of the ACI MTA FAD.

1.6 ERG commentary on the robustness of evidence submitted by Co-Don

The ERG has attempted to revise the company model to have inputs similar to those of the 1st AG report of the ACI MTA. This is imperfect but appears to suggest that the company model estimates roughly double the patient gains compared to the model of the 1st AG report of the ACI MTA. The cost effectiveness estimates of the ACI MTA also tended to worsen as the assessment progressed and publicly available time to event data for loss of response was incorporated. The company model structure may be too optimistic for the comparison with microfracture.

The company accepts that all the clinical effectiveness estimates for the model of its original submission are wrong and biased in favour of Spherox. It has provided a revised set of estimates for a subset of these. These still appear to be incorrect and biased in favour of Spherox.

The clinical effectiveness estimates for Spherox are little different from those of microfracture. The model estimates quite large QALY gains from Spherox compared to microfracture. These are almost entirely due to the assumption that all microfracture successes fail at year 5.

1.7 Summary of additional work undertaken by the ERG.

The ERG is limited to the company model structure and while it has made some revisions to this it cannot revise the model to reflect the full model structure of the model of the ACI MTA.

In the light of the ACI MTA FAD the ERG also limits the number of comparators. A 1st microfracture repair cannot be followed by a 2nd microfracture repair or by a 2nd ACI repair.

The ERG has revised all the clinical effectiveness estimates of the model, and has aligned the unit costs with the preferred set of unit costs of the ACI MTA FAD.

If all microfracture successes fail at year 5 the company model estimates the cost effectiveness of Spherox compared to microfracture to be £4-5k per QALY. It also estimates the cost effectiveness of MACI compared to Spherox to be £12-18k per QALY.

If microfracture successes are as durable as ACI successes the company model estimates that Spherox results in few patient gains relative to microfracture and its cost effectiveness is very poor. The cost effectiveness of MACI compared to microfracture also typically rises above £30k per QALY.

1.8 ERG conclusions

Spherox is clinically effective in the treatment of chondral defects, and the Phase II trial shows benefit maintained for up to [redacted] years. [redacted].

2 Introduction

Members of the Appraisal Committee who are familiar with ACI may wish to go straight to Section 2.4

2.1 Cartilage injuries

The ends of the bones and the inner surface of the patella in the knee are covered with articular cartilage. Articular cartilage should not be confused with the meniscal cartilages that are cushions of cartilage between the bones – when people talk of "cartilage problems" in the knee, they often mean the meniscal cartilage.

Normal "hyaline" cartilage is a rubber-like substance that is normally very smooth, promoting smooth frictionless movements of the joints and also acting as a shock absorber. It is formed mainly of a protein called type 2 collagen. Under the articular cartilage are the bones of the knee – femur in thigh, tibia below the knee, and the patella or knee-cap.

Cartilage has no blood vessels and has very limited ability to repair itself. Epidemiological studies show a relationship between knee injury and later development of osteoarthritis. In some people, this will lead in the long-term to a need for a knee replacement with an artificial joint, usually total knee replacement (TKR), though there can be partial knee replacement of just one side.

Loss of articular cartilage is referred to as a chondral defect, and loss of cartilage and bone as an osteochondral defect. Cartilage damage can be caused by injury, by various types of arthritis, or spontaneously in a condition called osteochondritis dissecans (OCD) in which a bit of bone and attached cartilage breaks off. Cartilage damage may also arise because of knee instability or abnormal loading, for example secondary to a ligament injury[1] or damaged meniscal cartilages.[2] Serious obesity may also affect knee cartilage.[3] Conversely, physical activity without injury may be protective.[4]

In young people the most common cause of hyaline cartilage damage is sporting injuries. Aroen and colleagues[5] reported that in patients having knee arthroscopy in Norway, injuries occurred in sport in 55%, in the home in 15%, at work in 12% and in road traffic accidents in 5%. In 13% the cause was unknown.

It should be noted that cartilage defects without any underlying bone involvement may not cause pain – there are no nerves in cartilage. The source of pain in knees with damaged cartilage is poorly understood but may come from many sources including ligaments, the joint capsule and the underlying bone.[6] So results from series of symptomatic patients may not be entirely representative of all people with cartilage damage. The commonest symptom is pain, with others being temporary locking of the knee in one position, and swelling. Pain and disability from symptomatic cartilage lesions have been shown to be as significant in magnitude as that from severe arthritis of the knee.[7]

The longer-term consequence of chondral injury is osteoarthritis (OA), which develops over time and often leads to a need for knee replacement. Knee replacement has been of great benefit to many people, by relieving the pain of OA, but it does not restore the full range of function in the knee, and replacements do not last forever. Failure is common after 10-15 years, and while a replacement can be replaced, second knee replacements are more difficult, about double the cost, and are accompanied by a greater risk of complications. Orthopaedic surgeons try to avoid doing knee replacements done before the age of 55 in OA. (In other forms of arthritis such as rheumatoid arthritis (RA), they may be done at younger ages but may last longer because people with RA are limited in other ways and put less stress on the new joint.) So a treatment for chondral defects that removes symptoms could be very useful even if it did not give a permanent repair, by acting as an interim solution till patients were able to have knee replacements.

The International Cartilage Repair Society (ICRS) has a scoring system for grading the severity of cartilage damage [8];
Grade 1: soft indentation and/or superficial cracks
Grade 2: small cracks or lesion extending down to under half of cartilage depth
Grade 3: deep cracks or gaps of over 50% of cartilage depth
Grade 4: cracks through the total thickness of cartilage down to the underlying bone
Grade 5: defects of the full thickness of cartilage involving the sub-chondral bone

Grading is done by arthroscopic examination. An arthroscope is a fibreoptic telescope inserted into the knee joint so that the surgeon can look at the injury.

2.2 Autologous chondrocyte implantation

The cells that produce cartilage are called chondrocytes. In autologous chondrocyte implantation (ACI), a small piece of cartilage is removed from the knee, and the chondrocytes are cultured the laboratory until they number millions. They are then put into the damaged area of articular cartilage

as a patch. The hope is that this patch will repair the damaged area and form a new layer of natural articular cartilage, called hyaline cartilage. Autologous means that the cells implanted in ACI come from the patient's own cartilage.

Chondrosphere or Spherox is the latest form of autologous chondrocyte implantation (ACI) to be appraised by NICE, and the fourth appraisal of ACI. The FAD (Box 1) from the third appraisal was issued on 4th October 2017. It does not specify any particular ACI product, but gives a general approval to ACI.

Box 1. FAD on ACI

FAD for ACI

Autologous chondrocyte implantation (ACI) is recommended as an option for treating symptomatic articular cartilage defects of the knee, only if:

- the person has not had previous knee repair surgery
- there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis)
- the defect is over 2 cm^2
- the procedure is done at a tertiary referral centre.

One point to note is that the restriction to people who have not had previous attempts at repair such as microfracture (debridement does not count as a cartilage repair procedure) is based on ICERS which were higher after previous repairs because ACI is less successful if the subchondral bone has been damaged. However those ICERS assume cell cost of £16,000 (the list price). The cell costs are one of the key drivers in the cost-effectiveness analysis, and a significantly lower price might produce acceptable ICERs.

One issue which will need to be clarified is the tertiary referral process. Referral could be based on MRI in the first centre, with both harvesting and implantation both done in the tertiary centre.

2.3 Treatments for chondral injury

There are several possible interventions after chondral injury

Conservative management

One option is no surgical treatment, but to use symptomatic relief, with or without physiotherapy. Three case series [9-11] reported high levels of return to activities after cartilage injuries after 14 years, 9 years and 9 years respectively. Messner and Maletius reported a case series of young athletes (mean age 25, range 14-38) who had no treatment. 14 years later, most (21 out of 28) had returned to activity and 22 had excellent or good function.[9] However despite lack of symptoms, most showed radiological changes suggestive of early osteoarthritis. The NICE guidance specifies "symptomatic articular cartilage defects of the knee", but in some people, symptoms resolve. However the cartilage defect will not, and they are likely to develop OA, and some will need knee replacement in later years.

The UK knee surgeons' consensus recommends that all patients being considered for ACI should have had physical therapy first, since that may relieve symptoms.[12]

Lavage and debridement.

In lavage, an arthroscope is inserted into the knee and saline is poured in through a cannula. This is usually done under general anaesthesia on a day case basis. The saline washes out loose debris which comes out through the cannula or is sucked out using a suction/shaving device. It is also thought to wash out compounds that cause inflammation.

Debridement is done under arthroscopic vision and is the removal of damaged cartilage or bone. It is not a repair procedure. Debridement and lavage are often done at the same time.

The evidence for effectiveness of debridement is sparse and mixed. One three-armed RCT of lavage alone, lavage plus debridement and a sham arm reported no difference at 2 years.[13] Another by Hubbard had methodological weaknesses, but reported that debridement and lavage was better than lavage alone.[14] The NICE intervention procedures guidance on lavage with or without debridement (IPG230) noted uncertainty about the efficacy of the procedure.[15]

ACI

ACI has been used since at least 1987.[16] The procedure has evolved over time, with different ways of implanting the chondrocytes into the chondral defect.

In the first generation of ACI, the cultured chondrocytes were placed in the defect, in liquid form, and then covered with a cap made from a patch of periosteum, the tough fibrous tissue that covers bones such as the tibia – ACI-P. This led to problems with pain at the periosteal harvest site in the immediate post-operative period, and a need for further procedures to remove overgrowth in the graft. It is now obsolete but comes up in some of the older Chondrosphere studies.

The second generation of ACI used a collagen cap (ACI-C) instead of the periosteal one, but still used cells in a liquid suspension

In the third generation of ACI, the chondrocyte cells are loaded or embedded, or "seeded", on to a porcine collagen membrane ACT-C or matrix (MACI – matrix induced chondrocyte implantation), with a patch cut to fit. These patches can be implanted by a less invasive form of surgery, by mini-arthrotomy, requiring less surgical time than ACI-C.[17] (Arthrotomy = opening of a joint). This has become the main method used.

The membrane used in MACI is composed of type I/III collagen, with a rough side wherein the chondrocytes are seeded and a smooth side which faces into the joint cavity.[17] The membrane is tough enough to be cut to shape or stitched in place, though it is more often glued in place.[17] The membrane is bio-degradable. The term "scaffold" is often used instead of membrane. However the membrane needs careful handling to minimize chondrocyte death during implantation.[18]

Box 2. The evolution of ACI

First generation	ACI-P. Liquid suspension of cultured chondrocyte cells placed in the defect covered with a cap made from periosteum.
Second generation	ACI-C. Liquid suspension of cells placed in the defect and covered with a collagen cap.
Third generation	The cultured cells are seeded on to a membrane or "scaffold" as in MACI (matrix associated chondrocyte implantation).
Characterized chondrocytes	Not all chondrocytes are equally good at producing cartilage. Some are more "chondrogenic" (cartilage-producing) than others. The most useful can be selected and are known as "characterized".
Fourth generation	Newer developments include the implantation not of cells that will form cartilage, but of tissue-engineered cartilage grown from autologous chondrocytes in the laboratory. Some of the chondrocytes used may come from cartilage from the nose or ear.

Spherox (formerly known as Chondrosphere and ACT3D) is a form of fourth generation ACI in which the cells are not only multiplied in the laboratory, but are persuaded to generate cartilage. Chondrocytes are harvested from healthy articular cartilage, cultivated for 8-10 weeks in the laboratory, and condensed into spheroids (chondrospheres) of cells plus cartilage. The 3-dimensional spheroids are then implanted into the defect. The Co-Don submission says that the spheroids adhere to

the defect (presumably to the subchondral bone) and that no cap or fibrin glue is required to keep the in place.
Spheroids of human autologous matrix-associated chondrocytes are licensed in Germany for the treatment of articular cartilage defects of the knee, hip, shoulder, elbow and ankle. Unlike MACI, the procedure does not require any non-human collagen scaffold.

Microfracture

The main alternative method of repair has been microfracture, in which small holes are drilled through the surface of the bone in the area of damaged cartilage. This allows bleeding from the bone marrow, and the blood carries stem cells into the area where the damaged cartilage has been debrided. These cells form scar cartilage called fibrocartilage, composed of type 1 collagen. This is regarded as being inferior to hyaline cartilage, being less hard-wearing and it is not expected to last as long.

Microfracture may be combined with the insertion of a collagen membrane to cover the microfracture clot, known as augmented microfracture.

Microfracture can be done arthroscopically (i.e. without opening the knee joint) and can be done at the same time as debridement and lavage.

Mosaicplasty

Mosaicplasty (sometimes called OATS – osteochondral autograft transfer system) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. The pieces are in little cylinder shapes and once transplanted, have an appearance not unlike a mosaic – hence the name. Mosaicplasty can only be used for small areas of damage because the transplanted sections have to come from elsewhere in the knee, usually the trochlea. (In some countries, allograft cadaver donor tissue is used, but this appears to be rare in the UK because of issues around local funding and arrangements for the sourcing of the allografts.)

Mosaicplasty appears to be little used now. In the ACTIVE trial [19] of ACI versus standard methods such as microfracture and mosaicplasty, few surgeons chose mosaicplasty.

Comparator ACIs.

In the last appraisal of ACI by NICE, three forms of ACI were appraised.

- The ChondroCelect ACI system from TiGenix, a form of ACI-C in which the cultured cells are combined with a biodegradable collagen I/III patch, with characterised chondrocytes.

ChondroCelect received European marketing authorisation in October 2009.[20] It was being marketed by Swedish Orphan Biovitrum, but following the initial negative NICE decision, production ceased, and ChondroCelect is no longer on the market

- The Matrix ACI system (MACI® – short for "matrix applied characterised autologous cultured chondrocyte implant") originally developed by Sanofi. The matrix refers to a collagen membrane into which the chondrocytes are loaded at operation. The Sanofi MACI was approved in Europe in June 2013.[21] This product was taken over by Aastrom Biosciences who changed their name to Vericel. They recently received FDA approval for their MACI product now being marketed in the USA. They do not at present have any manufacturing facility in Europe, so the EMA has suspended their European licence. However we have heard that the EMA will be inspecting the US production facility and that cells may be provided to Europe from there. (Note that MACI is used both to refer to third generation ACI, and as a trade name.)
- ACI using cells cultured in the John Charnley Laboratory, an NHS laboratory at the Robert Jones and Agnes Hunt (RJAH) Orthopaedic Hospital in Oswestry, England. The facility has cultured and provided autologous chondrocytes (OsCells) for use in ACI since 1997. The facility has a Hospital Exemption Licence under the advanced therapy medicinal products regulations that enables OsCell to supply chondrocytes for use in ACI. This is the only NHS facility that currently cultures cells for use in ACI. NICE refers to OsCells as "traditional ACI".

2.4 Some decision issues

As noted in the ACI FAD, ACI is less successful in patients who have had previous attempts at repair, usually by microfracture, which damages the bone immediately under the cartilage (subchondral bone). When comparing results of Spherox and other forms of ACI, the proportions with previous repair attempts needs to be considered.

There may be a question about how soon cartilage defects should be treated. In the TIG/ACT trial of ACI versus microfracture, outcomes were better in those treated within three years of symptom onset compared to those with longer duration.[22] However the 3-year division is somewhat misleading, because the under 3-year group had an average duration of injury of just under one year, and the over 3 years group had average duration of almost 8 7.8 years. The groups also differed in other ways. Mithoefer and colleagues have also reported better results with ACI sooner after injury, in football players.[23] Harris and colleagues also concluded that results were better in patients with shorter duration of symptoms and fewer prior procedures.[24] So duration of injury should also be considered when comparing results.

Patient factors.

The patient group, as stated in the scope from NICE, is "people with an articular cartilage defect". The EMA approval mentions adults and symptoms. The NICE FAD states that ACI should not be used in advanced OA.

There are three issues here: adults, symptomatic, and defining advanced OA.

Adults. In most past trials, patients had a mean age of 32, range 16 to 49, with about 60% men. In most cases, the cartilage damage was due to injury, usually from sport. However there are now several trials in teenagers (ages 15-17). Some studies of Spherox included patients as young as 15.

Symptoms. Some people with chondral injuries have symptoms which resolve. The UK consensus summarised in Box 3 below, would restrict ACI to people with symptoms and with higher grade lesions. As the statement recognises, some people may have symptoms relieved by physiotherapy. However physiotherapy cannot repair chondral defects, so this group will still be at risk of progression to osteoarthritis.

Box 3. UK Cartilage Consensus [12]

The surgical management of symptomatic articular cartilage defects of the knee: consensus statement from UK knee surgeons.

The statement notes variations in provision of repair of articular cartilage in the knee, and financial constraints on the more expensive treatment options.

The consensus relates to management of an isolated chondral lesion in a knee that is free of other defects, or in which these have been corrected. Key points include;

- Surgical treatment should be considered for symptomatic lesions of ICRS grade 3 or worse.
- Microfracture leads to fibrocartilagenous scar tissue that has poorer biomechanical properties that normal hyaline cartilage, and this repair tissue degenerates. Short-term improvement in symptoms does not persist.
- Mosaicplasty can give good short-term results in small lesions but longer-term results are poorer. It is not suitable for larger lesions, or for patellar defects.
- In small defects, less than $2cm^2$, microfracture, mosaicplasty and ACI may all be considered.
- For lesions > $2cm^2$, cell therapy (ACI) is the most effective treatment based on current evidence

- Outcomes are poorer in smokers, patients with BMI>30, and those with a long duration of symptoms
- When ACI is considered appropriate, it should be first-line treatment because results are poorer if it is used after failure of other procedures
- Physical therapy may be effective in controlling symptoms and should be provided before surgery is considered.

Osteoarthritis.

NICE considered the OA issue and chose a form of words in the FAD which may lead to debate:

"there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis)"

The most common method for assessing structural changes in knee osteoarthritis is plain radiography, graded using the Kellgren-Lawrence (K-L) classification.[25] 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.[26-31]

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.[27, 29] 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.[32]

The boundary between K-L grade 2 and 3 is often difficult to define as the interpretation of 'possible' and 'definite' joint space narrowing can be very subjective.[33] 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.[32] Patients with an isolated chondral lesion and no OA may, simply from the result of loss of joint space due to the chondral lesion, be mistaken for having OA based on the K-L grade. The ERG therefore feels that the recommendation made for defining OA in the NICE ACI FAD is a good and pragmatic solution.

3 The Co-Don submission.

Co-Don have been unfortunate in the timing of the Spherox appraisal. They have based their submission largely on their single RCT which compared Spherox with MF. However, NICE has now approved ACI in place of most MF. So the key comparators are the other forms of ACI, and in particular Vericel's MACI, because it has the only licence in Europe, albeit temporarily suspended. MACI is used by Vericel as a trade name, but it is also used as a general term to describe third generation ACI. When referring to the Vericel product, we will use VerMACI.

3.1 Manufacturer's description of health problem.

Co-Don provide a concise but accurate description of chondral injuries, making the key points;

- Articular cartilage has very limited self-repair capacity
- Chondral injuries are common, especially after sporting or occupational injuries
- Because the chondral lesions don't heal, they lead to osteoarthritis
- The people who sustain such injuries are often in their 20s and 30s
- So they are much too young for knee replacements
- We need interventions to repair the chondral injuries to relieve symptoms and to prevent, or at least delay, progression to OA.

3.2 Manufacturer's description of current services

The Co-Don submission correctly notes that in the current clinical pathway in the UK, people only progress to ACI once conservative treatment, such as physiotherapy and analgesia has failed. This is in line with the UK Knee Surgeons consensus statement in Chapter 1. The submission also noted the then draft FAD on ACI, which recommended ACI as first line surgical treatment following conservative care, with the restrictions reported in Section 2.2 above.

So Co-Don provided a correct overview of an evolving situation, since it had to be written before the final FAD was released.

However, the submission does not give an account of current provision of ACI in the UK. The NICE guidance of 2004 recommended ACI only in research, and the 2015 ACD repeated that recommendation. So very little ACI has been done.

The approval by NICE of ACI, subject to certain restrictions, is likely to be welcomed by orthopaedic surgeons in the UK. Commissioners of care will be expected to fund ACI. Patients with chondral defects will look forward to an effective treatment.

Unfortunately, provision of cells may be a problem. TiGenix has discontinued production of ChondroCelect. They may resume but that would take time, and marketing authorisation was discontinued. The licence for Vericel MACI is currently suspended because they have no European production facility, but may be reinstated after the EMA has inspected the production site in the USA. We do not know if Vericel will open a new facility in Europe.

OsCells is authorised to produce cells only for use in the RJAH Hospital in Oswestry. They can and do accept referrals from elsewhere but their capacity is limited.

Other NHS units may seek to develop cell production facilities but would have to obtain MHRA approval and developing the facilities would be a lengthy and difficult process.
So in the short term, there may be a mismatch between supply and demand.

3.3 Co-Don definition of decision problem

The Co-Don summary of the decision problem is similar to the NICE scope, except that Co-Don consider that some of the comparators were inappropriate, including osteotomy and mosaicplasty. The ERG agrees with the Co-Don position. Mosaicplasty is little used in the UK and we think it would be used only for small lesions.

However following the recent MTA, the NICE scope is out of date, and microfracture is no longer a comparator. So the decision problem as defined by Co-Don is also out of date – the timing was unfortunate.

The outcomes in the Co-Don decision problem match the NICE scope.

The NICE scope mentions "people" with no age restriction. The EMA SPC states that "safety and efficacy of Spherox in children aged 15-18 are not established".[34] However the Co-Don submissions notes that two studies, cod 16 HS 16 (2012) and cod 16 HS 17 paed (2016) (with some overlap of patients), have shown that Spherox was considered safe and effective in adolescents of 14 to 17 years of age. The EMA approved a paediatric investigation plan in November 2012. It appears that only an interim analysis of these studies has yet been carried out, so presumably data will be provided to EMA in due course.

The SPC from the EMA says "Application of Spherox in obese patients is not recommended." No reason is given, but both trials of Spherox excluded patients with BMI >30. This may cause problems because the commonest cause of chondral injury is sport, and in sports such as rugby, many players have BMIs over 30, especially the forwards. However they are muscular rather than obese. A blanket restriction by BMI would be inappropriate.

The SPC recommends a few other restrictions;

- Primary (generalized) osteoarthritis
- Advanced OA of the affected joint, defined as exceeding Kellgren Lawrence grade 2
- Other joints. The SPC states that safety and efficacy are not established beyond the patella and femoral condyles.

3.4 Intervention: Manufacturer's description of Spherox

As noted above, Spherox consists of implants of both chondrocytes and the cartilage they have produced in the laboratory. The Co-Don submission reports that Spherox received a marketing authorisation from the European Medicines Agency (EMA)[35] in July 2017, but also that it has been used, with a marketing authorisation, in Germany since 2004, in around 11,000 patients in 120 orthopaedic departments. It has also been used in five other European countries.

However, the regulatory situation changed, and in order to comply with the regulations on tissue-engineered products (Article 2 (1) (b) of Regulation 1394/2007/EC) Chondrosphere became subject to a centralised authorisation procedure, which required a clinical trial.

The approved indication is for the repair of symptomatic articular cartilage International Cartilage Repair Society (ICRS) grade III or IV defects on the femoral condyle and on the patella, for defects of up to 10 cm^2 in adults.

The EMA verdict was not unanimous, and 16 members expressed dissent (EPAR report)[35], and argued that Spherox was "not approvable due to a negative benefit/risk ratio". Reasons for dissent included;

- Only clinical non-inferiority to MF has been shown
- Pain medication could have been a confounding factor
- Efficacy based on MOCART structural endpoints was not proven, and most of the seven biopsies after Spherox showed mixed fibrous tissue, not hyaline cartilage

- The number of non-responders in both the trials was >30%, and since Spherox required two operations compared to one for MF, benefit for patients was not demonstrated.
- The dissenters was also concerned about production processes and whether problems therein were related to non-responder rates.

Note that at the time Spherox was being considered, only 12 month data from the COWISI trial were available, and the dissenters stated that the 24 month data were required before the benefit/risk assessment could be completed. So some may not now dissent.

The price of the spheroids is given as £10,000, and this is not flagged as confidential. It includes transportation costs. Harvesting and implantation costs are added and Co-Don have used the costs from the recent MTA, adjusted for inflation. This is despite an assertion (page 19) that Spherox requires less invasive surgery for implantation, arthroscopically or by mini-arthrotomy, which may result in less theatre time.

However MACI can also be done by mini-arthrotomy. (And arthroscopically, but cell viability and speed are better when ACI is done by mini-arthrotomy than arthroscopically.[36]
Several of the case series from Germany report that Spherox can be implanted arthroscopically, so we can accept that a slightly shorter operation is required, perhaps saving 10 minutes of theatre time. This will have little effect on overall costs.

3.5 Clinical effectiveness - trials

The Co-Don submission presents the results from two trials, one Phase II and the other phase III, but mentions some earlier case series in an appendix. They carried out systematic searches for studies, using what we consider to be reliable search strategies. No systematic reviews of Spherox were found.

The Phase II trial, called HS14, was conducted prior to the Phase III trial and aimed to identify the optimal strength of Spherox by comparing three arms with different doses. There was no non-Spherox arm.

The Phase III compares Spherox with MF. This trial, which provides evidence for the modelling, is NCT01222559, now known as COWISI, but formerly called HS13. It is described in the submission as:
Phase III clinical trial designed to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product Spherox with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm^2

The COWISI trial

This is summarised in Table 1, adapted from Table 3 of the Co-Don submission

Table 1 Summary of the COWISI trial

Study	NCT01222559 (COWISI)				
Study design	Prospective, randomised, open label, multicentre Phase III clinical trial				
Population	The analysis population comprised 102 patients (41 women, 61 men) aged 37 ± 9 years, with ICRS grade 3 or 4 chondral defects on femoral condyles.				
Intervention(s)	Implantation of Spherox into the cartilage defect. There are two study operations: harvesting of chondrocytes at arthroscopy and, after approximately 2 months, implantation of Spherox.				
Comparator	Microfracture				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Reported outcomes specified in the decision problem	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from Day 0 (baseline for both treatment groups = pre arthroscopy assessment) to assessment at 24 months, compared between Spherox and microfracture. Overall KOOS including 5 subscores (pain, knee function including long-term function, activities of daily living, other symptoms and quality of life). Activity levels, avoidance of osteoarthritis including knee replacement, adverse effects of treatment, health-related quality of life				
All other reported outcomes	MOCART (MRI Score), ICRS and ICRS II Visual Histological Assessment Score, Bern Score, Change of ICRS/IKDC, Change of modified Lysholm Score. Days of absence from work				

As in other trials, microfracture was performed by the method developed by Steadman et al.[37]

The entry criteria excluded people with BMI over 30, but Table 7 reports a range of BMIs up to 31.2. Further follow-up visits are planned at 36, 48 and 60 months. The current results were from visits at 3, 12, 18 and 24 months, but we focus on the 24 month results. The exclusion criteria in Table 5 also list radiological signs of OA as an exclusion but according to Table 8, four people with OA were included.

The KOOS assesses pain, symptoms, activities of daily living, sport and recreational activities, on a scale of 0 to 100, where 100 is best.

The MOCART score (magnetic resonance observation of cartilage repair tissue) is based on imaging by MRI (magnetic resonance imaging). It was recorded at 12 months and 24 months, but our focus is

on the 24 month data because that gives more time for the implanted cartilage to mature. MOCART has subscores that look at issues such as whether the chondral defect (the gap of missing articular cartilage) has filled completely, and at the smoothness of the surface, which could be an indication of whether the gap has been filled with hyaline cartilage or less durable fibrocartilage.

The ICRS scores are based on inspection of the repair by arthroscopy, and on the histology of biopsies of the repair. Only a minority of patients had arthroscopy – 10 from the Spherox arm and 7 from the microfracture arm. The Bern score also examines the composition of transplanted cartilage.
The Lyshom score is based on patient reports on 8 aspects: pain, limping, locking, stair-climbing, need for supports, instability, swelling and squatting. It has a range 0 to 100 (best),
Days of absence from work is useful, but another option, not used in this trial, is time to resumption of previous activities, which is particularly relevant to sportspeople, who may be able to work but may not be able to play sports again. Some recent studies have used return to sport as an outcome.
IKDC (International Knee Documentation Committee) is another symptom score with range from 0 (worst) to 100 (best), based on function, symptoms, and range of motion.

Quality
As assessed by the Cochrane risk of bias score (Appendix 1), COWISI was a good quality trial though blinding of intervention was impossible. The submission notes that MRI and follow-up biopsies were assessed centrally by blinded independent radiologists and pathologists, respectively. However the key outcomes are neither radiological nor pathological, but symptoms. One source of bias may have been avoided because (pages 28-20)

"*Patient-Reported Outcomes data were entered directly by the patients into an ePRO (electronic Patient-Reported Outcome) system specifically designed for the trial."*

That removes the chance for non-blinded clinical staff to influence patient responses.
There were 102 patients randomised, not far short of the 118 in the TIG-ACT trial[38], but less than the 144 in SUMMIT.[39]

Baseline matching was good, [redacted]. The table (Table 7) of baseline characteristics does not provide details of duration of injury and proportions having previous attempts at repair. The defect sizes after debridement were similar: [redacted].

There were what were described as major protocol violations in [redacted] in the Spherox group and [redacted] in the MF group. These included some violations that may not seem major. They included (CSR pages 82-83):

[redacted]

The trialists seem to have been quite strict.

The sample size was based on showing non-inferiority which seems odd. We would have expected the trial to be aimed at showing that Spherox was better than MF, since that is what other trials of ACI aimed to do. Non-inferiority was taken to be shown if the KOOS score with Spherox was not 8.5 points lower than with MF. A clinically meaningful difference in KOOS is usually taken to be 10 points or more, but some researchers accept 8 as a meaningful difference.

In a non-inferiority trial, one should justify the choice of the non-inferiority margin, which corresponds to some loss of efficacy that might be accepted, with regards to other benefits, like safety ones, that the new intervention might have over the compared intervention. There is no such justification in the Co-Don submission.

Pages 42-43 of the Co-don submission outlines the testing for non-inferiority, and elsewhere there are references to power for non-inferiority. [redacted]

It may be that the aim was to show similarity with other trials of ACI versus MF, which do not usually show differences in the early years, but COWISI will be collecting data at 5 years, by which time an effective form of ACI may be giving better results than MF. So we might have expected the longer-

term aim of COWISI being to show superiority over MF. This is mentioned later, just after Table 14, where it is stated;

"The study was designed to test the non-inferiority and possible superiority of Spherox"

Results

Table 2 Results of COWISI trial

	Spherox	MF
Baseline KOOS	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
24 month KOOS	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
Change baseline to 24 months	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
Baseline MOCART	Not reported	Not reported
24-month MOCART	[redacted]	[redacted]

In the text below Table 16, we are told that the ANCOVA difference in change in KOOS is [redacted], which does not fit with the 24-month figures of [redacted]. Shortly below, we are told that ANOVA analysis gives figures of [redacted] for Spherox and [redacted] for MF, a difference of [redacted]. [redacted]

KOOS subscore results are given in Co-Don Table 17, [redacted], but with p values not given. [redacted]. Co-Don Table 18 gives changes from baseline in KOOS subscores, without p values, but reporting in the text that the improvement in one subscore, function in daily living, [redacted] and median changes [redacted] for Spherox and MF respectively. Since the [redacted], we do not think the subscore analysis adds anything of note.

The MOCART scores (Co-Don Table 20) at 24 months show [redacted]. MF gave slightly better results but the difference had confidence interval (presumably 95% CI, but not stated) of [redacted]. The submission notes (page 112 and table 29) that there was "at most - a

very weak correlation" between MOCART and KOOS scores. Some figures in Table 29 appear to have been misplaced.

ICRS results at 24 months were available from only 10 Spherox and 7 MF patients. Arthroscopic assessment showed no significant differences between arms. Histological assessment is reported in Co-Don Table 22, reproduced in Table 3.

Table 3 Cartilage repair assessment: numbers of patients and biopsy results

	Spherox	MF
Hyaline	[redacted]	[redacted]
Mixed hyaline and fibrocartilage	[redacted]	[redacted]
Fibrocartilage	[redacted]	[redacted]
Fibrous tissue	[redacted]	[redacted]

The Bern score results showed no difference.

The IKDC examination has four grades. The baseline and 24 month results are shown in Table 4. The text states that the [redacted] but no statistical test is provided. The SE of the [redacted] for Spherox at 24 months is 4.7%, and for the [redacted] for MF is 6.3% so the CIs overlap. (ERG calculations).

Table 4 IKDC Knee Examination results

	Spherox		Microfracture	
Grade	Baseline (47)	24 months (48)	Baseline (48)	24 onths (49)
A. Normal	[redacted]	[redacted]	[redacted]	[redacted]
B. Nearly normal	[redacted]	[redacted]	[redacted]	[redacted]
C. Abnormal	[redacted]	[redacted]	[redacted]	[redacted]
D. Severely abnormal	[redacted]	[redacted]	[redacted]	[redacted]

There are 10 IKDC Current Health Assessment subscores, [redacted] versus [redacted] on a scale of 0 to 100. Given the number of tests this may be a chance finding.

The Lysholm scores [redacted].

The proportions of recruits improving by 10 or more points on the KOOS score ("responders") at 24 months were [redacted].

Overall, in the planned analysis, there was [redacted].

Once the results were available, an alternative analysis was carried out, using a one-sided confidence level of alpha = 0.05. [redacted]. The ERG is doubtful as to whether this post-hoc analysis with a changed alpha represents good practice.

In the alternative analysis, superiority was also reported for change in the physical functioning score of the IKDC current health assessment subscore, but no figures or p value were provided.

Additional analyses

The results for two age groups, 18-34 and 35-50 years, were compared. Both age groups are reported to have had significant improvements, but neither baseline KOOS scores or changes from baseline are not given, only 24 month scores.

[redacted].

The Clinical.Trials.gov registration includes the outcome of days of absence from work (employment) and/or days of inability to follow usual activities during the last year or since the last visit, respectively, and time point when patient was back to work and/or to follow usual activities, but this is not reported in the submission.

Defect sizes

The COWISI trial included patients with (page 23 of Co-Don submission) defect sizes after debridement of >1 cm^2 to <4cm^2. The NICE ACI FAD recommends that ACI should be used only for lesions greater than 2cm^2. We therefore asked Co-Don as part of the clarification process, to split the COWISI results by defect size. We requested this breakdown because it is known that the effectiveness of microfracture declines as lesion size increases, and in our clarification request we hypothesised that the microfracture results in the smaller defects (<2 cm^2) might be better relative to Spherox, than in larger lesions. So the overall results of COWISI might have been missing a greater effect in the group to which the NICE FAD on ACI restricts it.

The results are in Table 5 – see row in bold. Figure 1 shows the flowchart for participants with lesion size >2cm^2. [redacted].

Table 5 Changes in KOOS score by defect size

KOOS score	*24 months*			
	Strata Defect size and treatment group			
	ACT:1-≤2cm²	*MF:1-≤2cm²*	*ACT:>2-4cm²*	*MF:>2-4cm²*
KOOS (overall)	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]
Lower quartile	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Upper quartile	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]

These figures are based on the ITT populations. Numbers are quite small (see figure 1), and fall even further if those with protocol violations are removed. In their response to clarification questions, Co-Don reported that non-inferiority was shown between Spherox and MF in both defect size groups.

Figure 1 Flowchart by size of defect.

Other clarification responses.

Co-Don explained how they had calculated failure rates in the NMA, when there were no failures in COWIS and SUMMIT;

The median RR of 0.9894 was calculated assuming that in each arm 0.5 patients experienced the event. This approach was used per the NICE DSU document (Dias et al. 2016; reference provided with this submission) which recommends this in the case that no events are observed in one arm of the trials. Due to the larger sample size of the SUMMIT trial, a RR in favour of MACI was obtained. However, for the purpose of the economic model, 0 events were assumed for both interventions.

The Phase II trial (NCT01225575)

The aim of this trial was to compare three doses of Spherox. There was no control group. It recruited people with defects of 4-10 cm^2 in area, and about two-thirds had patellar defects. So the group studied is different from those in the COWISI trial, which had no recruits with lesions that large and was almost entirely of condylar defects. The restriction to large defect sizes was stated (Becher et al 2017[40]) to be because ACI was already regarded as the standard of care for medium (3-4 cm^2) defects.

The trial is summarised in Table 6, adapted from Table 4 of the Co-Don submission.

Table 6 Summary of dosages trial

Study	Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm^2) with 3 different doses of Spherox in subjects with cartilage defects of the knee (Trial no. cod 16 HS 14)		
Study design	Dose-response study.		
Population	Males and females between ages of 18 and 50 years with an isolated single cartilage defect of the knee joint		
Intervention(s)	Spherox Group A:patients receiving 3-7 spheroids/cm^2 Group B:patients receiving 10-30 spheroids/cm^2 Group C: patients receiving 40-70 spheroids/cm^2		
Comparator(s)	Not applicable		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	No
Rationale for use/non-use in the model	Not used in the model as not comparison with microfracture that could be included in the network meta-analysis.		
Reported outcomes specified in the decision problem	Change of overall KOOS from baseline to final assessment at 12 months after implantation. Follow-up visits are planned at 24, 36-, 48- and 60-months.		
All other reported outcomes	• Changes in KOOS • MOCART (magnetic resonance observation of cartilage repair tissue) • Modified Lysholm score • IKDC (International Knee Documentation Committee) knee examination form • IKDC current health assessment form • IKDC subjective knee evaluation form • Bern score • International Cartilage Repair Society rating		

An unusual feature of this study, which has been published in part (Niemeyer et al 2016 [41]with the 12-month follow-up, Becher et al 2017 [40] with safety data) in that 63% of chondral defects were on the patella and only 37% on the femoral condyle. Patellar lesions tend to do less well than femoral condyle ones. Results are not provided separately for patella and condyle.

The trial appears to be well-designed, but for our purposes the lack of a control group reduces its value, and 30% withdrew prematurely. [redacted]. One entry criterion was defect size 4-10 cm^2 but the mean defect size was 5.6 cm^2 and only 10 of the 75 patients had 7-10 cm^2 defects.[40] The table of baseline characteristics gives no details of duration of injury or of previous attempts at repair. The groups were well-matched at baseline.

There were [redacted], especially in the high dose group, sometimes due to inadequate cell proliferation in culture. The rest include failure to attend visits or to complete data collection.

The final results showed no important difference amongst the three groups, so we only report the whole group results here.

The KOOS score [redacted].

No analysis by duration of defect, or by history of previous repair attempts, was reported, but at clarification stage, Co-Don provided data showing no difference by duration of injury;

"Due to the study design of this Phase II dose confirmation study, the results are based on Spherox data only. For a total of [redacted] treated patients, the 4 year follow-up analysis yielded the following results:

- *< 1 year: n=[redacted]; mean ± SD,* [redacted]
- *>1 year: n=[redacted]; mean ± SD,* [redacted]"

The ERG identified the article by Becher et al[40] presenting the safety outcomes. We used this reference, that was not included in the Co-Don submission (it was published on-line on 12th May, perhaps too late), to check the results from the phase II RCT in the submissions against those in this manuscript. The aim of this paper was to report the safety outcomes at 36 months post treatment so no effectiveness outcomes were presented. The occurrence of severe adverse events (AE) over time were described consistently with the Co-Don submission together the baseline characteristics of included patients. In the Co-Don submission, adverse events in the trial were reported at 12 and 48 months, meaning that the ERG could not compare table 44 of the submission against the Becher et al. paper. Treatment-related AEs were infrequent – [redacted] arthralgia and [redacted] of chondropathy (cartilage disease).

Meta-analysis

Section B.2.8 provides a meta-analysis of the phase II and COWISI trials, but since these recruited mutually exclusive groups, the meta-analysis does not seem to add much.

ERG comments on Summary by Co-Don

Section B.2.12 states that "*Spherox is a fourth generation ACI and represents a marked improvement over microfracture*". This is not what the evidence summarised above shows. A number of statements are made by Co-Don about the comparison with MF. These are in italics below with our comments added

Spherox demonstrates the following improvements over MF:

- *Spherox aims to produce hyaline-like cartilage whereas MF is associated with the production of fibrocartilage which is inferior cartilage.* ERG comment: this was not shown in the COWISI trial, as reported in Table 3.

- *Spherox is shown to be more effective than MF across age categories studied.* ERG comment: Spherox was not shown to be more effective than MF.

- *Spherox can be used for large defects (up to 10 cm^2) whereas MF is generally used on smaller defects (1-4cm^2)* ERG comment: This comment is fair, because the larger the defect, the poorer the result with MF. However Co-Don did not provide any comparison with MF in defects larger than 4cm^2.

- *Spherox is associated with fewer serious adverse effects than MF.* ERG comment: There is a little support for this statement. In the Spherox arm of the COWISI trial there were no serious AEs related to the procedure. In the MF arm there were three AEs possibly related to the procedure, one deep vein thrombosis, one arthralgia and one adhesions.

- *Spherox may reduce the following complications because of the autologous cells used in the procedure:*
    - *Rejection and incompatibilities – where patients may require further procedures*
    - *Viral contaminations*
    - *Overcomes any objections to the procedure on religious grounds - no porcine derived collagen membrane*

ERG comment: none of these comments are relevant to a comparison to traditional MF, though the last might be if MF is used with a cap, or when Spherox is being compared with older forms of ACI. (Allografts were not included amongst the comparators.)

- *Using Spherox as first line surgical treatment before MF could be more effective than using MF 1st line before Spherox.* ERG comment: no evidence has been produced to support this statement because both the Cowisi and the Phase II trial excluded patients who had had previous MF. Based on research on other forms of ACI, we expect it to be true. However the FAD on ACI recommends ACI as first line in defects greater than 2 cm^2 so this comment is now superseded.

3.6 Clinical effectiveness - network meta-analysis

The ERG has appraised the methodology of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency. The NMA used only two outcomes, proportion of responders and failures (defined as requiring further surgery). KOOS is not used, despite being the primary outcome in the COWISI trial.

Baseline characteristics of included studies

In Table 7, we show the baseline characteristics of the three trials included in the Co-Don NMA.

Co-Don provide the results of the NMA, and then report the assessment of heterogeneity based on the key studies characteristics in section B.2.9.3. The ERG believes it would have been more appropriate to do the heterogeneity assessment prior to running the NMA, because we think this should have led to a decision not to undertake the NMA. Note that the Co-Don review of heterogeneity does not consider one of the most important factors, namely whether patients had had previous attempts at repair.

Table 7 Baseline characteristics of the three trials included in the Co-Don NMA

Variable	COWISI		SUMMIT		TIG/ACT	
Study sponsor	Co-Don		Sanofi (Vericel)		TiGenix	
Region/Country	EU: Germany and Poland		EU: Czech Republic, France, Netherlands, Norway, Poland, Sweden, UK		EU: Belgium, Croatia, Germany, Netherlands	
Number of centres	11		16		13	
Study period	Dec 2010-February 2017		Began May 2008		February 2002-January 2008	
Compared interventions	Spherox	MF	MACI	MF	ChondroCelect	MF
Sample size	52	50	72	72	57	61
Age ±SD	36 ±10	37±9	34.8 ±9.2	32.9 ±8.8	33.9±8.5	33.9±8.6
Male sex (%)	33 (63.5)	28 (56.0)	45 (62.5)	48 (66.7)	35 (61)	41 (67)
BMI (kg/cm2) ±SD	25.7 ± 3.3	25.8 ± 3.0	26.2 ± 4.3	26.4 ± 4.0	28 (49%) and 26 (46%) with a BMI≤25 and>25 to ≤30 respectively	31 (51%) and 24 (39%) with a BMI≤25 and >25 to ≤30 respectively
Lesion size cm^2	2.2 ± 0.7	2.0 ± 0.8	4.9 ± 2.8	4.7 ± 1.8	2.6 ± 1.0	2.4 ± 1.2
Previous repair procedures affecting subchondral bone n (%)	[redacted]		marrow stimulation techniques (34.6%),		14% (MF 5, drilling 3, abrasion 1)	7% (MF 1, drilling 2, abrasion 1)
Duration of symptoms (years)	[redacted]	[redacted]	5.8 (0.05-28.0)	3.7 (0.1-15.4)	1.97	1.57
Type of lesions	Isolated ICRS grade III or IV single-defect chondral lesion on femoral condyle		Cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC) and/ or trochlea		single grade III to IV symptomatic cartilage defects of the femoral condyles	
Outerbridge grade n (%)						
III	[redacted]	[redacted]	21 (29.2)	15 (20.8)	10 (18)	16 (26)
IV	[redacted]	[redacted]	51 (70.8)	57 (79.2)	47 (82)	45 (74)
Location n (%)						
Medial femoral condyle	52 (100)	49 (98)	54 (75.0)	53 (73.6)	57 (100)	61 (100)

Lateral femoral condyle			13 (18.1)	15 (20.8)		
Trochlea	0	0	5 (6.9)	4 (5.6)	0	0
Origin n (%)						
Acute trauma	19 (36.5)	24 (48)	33 (45.8)	45 (62.5)	NA	NA
Chronic degeneration	1	[redacted]	18 (25.0)	9 (12.5)	NA	NA
Osteochondritis dissecans	none	[redacted]	8 (11.1)	12 (16.7)	NA	NA
Unknown	none	[redacted]	9 (12.5)	6 (8.3)	NA	NA
Other	32	[redacted]	4 (5.6)	0	NA	NA
Baseline KOOS score						
Overall	[redacted]	[redacted]	NA	NA	56.3 ± 13.6	59.5 ± 14.9
Pain	[redacted]	[redacted]	37.0±13.5	35.5±12.1	62.1 ±18.73	65.5 ±17.1
Function	[redacted]	[redacted]	14.9 ± 14.7	12.6 ± 16.7	NA	NA
Concomitant surgery	0	0	36%	31%	7%	11%

Table 8 Results of MF in the three trials.

	Response				Failure	
Trial	Definition	KOOS score		Responders, n/N (%)	Definition	Failure, n/N (%)
		Baseline	24 months			
COWISI	At least 10-point improvement on overall KOOS score	[redacted]	[redacted]	[redacted]	Objective clinical findings by the investigator, which are directly correlated with subjective patient complaints resulting in a deterioration of the subjective clinical outcome as assessed by the total KOOS and the 5 KOOS	[redacted] at 24 months

					subscores. Or need for revision surgery.	
SUMMIT	At least 10-point improvement in both the KOOS pain and function subscales	Pain: 35.5 ± 12.1 Function: 12.6 ± 16.7	Pain: 70.9 ± 24.2 Function: 48.7 ± 30.3	49/72 (68.1)	After week 24, a patient and physician global assessment result that was the same or worse than at baseline, a <10% improvement in the KOOS pain subscale, physician diagnosed failure ruling out all other potential causes, and the physician deciding that surgical retreatment was needed	2/72 (2.8%) at 24 months
TIG/ACT	Overall KOOS of at least 10 and/or an increase from baseline of at least 10 in at least 3 of the 4 KOOS subdomains and/or an improvement from baseline in the degree of knee disorder severity of at least one category or a decrease from baseline of at least 20 points in VAS pain score and/or an improvement in the degree of knee disorder severity of at least one category.	Overall: 59.5 ± 14.9 Pain: 65.5 ±17.1	NA	31/51 (61%) at 36 months. (Note error in Table 3 of Saris 2009 – correct denominator is 51)	If the surgeon decided that reintervention in the index lesion was necessary because of the persistence or recurrence of symptoms	7/61(11.5%) at 36 months About 10% at 24 months (from graph)

The Co-Don critique of their NMA (pages 81-82 of their submission) is quite rigorous, gives several reasons why the NMA was inappropriate, and does cast doubt (page 83, last paragraph) on their comparability.

The ERG would phrase this more strongly. There is considerable heterogeneity in the baseline characteristics across studies that were included in the NMA as shown in Table 7.

The studies were conducted over different time periods and settings. There could be variations in techniques for both MF and AC depending on the practice and experience of centres, especially given the long experience with Spherox in Germany.

There were differences in inclusion criteria across studies particularly with regards to the baseline KOOS score, much lower in the SUMMIT trial, and the lesion size, much larger in SUMMIT. This led to differences in baseline characteristics of patients across studies for these two variables.

Because the SUMMIT trial included patients with moderate to severe KOOS pain scores (<55), this resulted in a major imbalance in KOOS between SUMMIT, and COWISI and TIG/ACT. The KOOS score at baseline appears to be an effect modifier for one of the outcomes used in the Co-Don NMA, namely the proportion of responders with responders being defined as having at least a 10-point improvement in one or several KOOS subscales. It is likely that the achievement of response was easier with a lower KOOS score at baseline, as in the SUMMIT trial, compared to higher KOOS scores at baseline, as in COWISI and TIG/ACT.

The SUMMIT trial included patients with a minimum lesion size of $3cm^2$, which also results in a considerable imbalance in the mean lesion sizes at baseline (between [redacted] in COWISI and TIG/ACT vs 4.7-4.9 cm^2 in SUMMIT). The lesion size is an effect modifier because there is evidence suggesting that ACI has a better outcome compared to MF in people with larger lesions, in which MF is less successful (for review see Mistry et al 2017[42]). So one might expect the MF group in SUMMIT to do less well than the MF group in COWISI.

However the most important difference is the absence of previous attempts at repair in the COWISI patients, whereas 35% and 14% of the ACI groups in SUMMIT and TIG/ACT had had previous repair attempts, mainly MF.

One way of assessing heterogeneity is to compare the results of MF in the three trials, as in Table 8. The proportion of responders was [redacted] in COWISI ([redacted]) than in the other two trials: SUMMIT 68% and TIG/ACT 62%. The proportions of failures also varied. This provides more evidence that the patient groups were different, and that an NMA might have been inappropriate.

The OA criteria in the three trials varied, as shown in Table 9.

Table 9 Osteoarthritis criteria in the three trials.

	Criteria regarding osteoarthritis in the three trials
COWISI	Exclusion criteria: Radiological signs of osteoarthritis, taking specific osteoarthritis drugs such as chondroitin sulphate, diacerein, N-glucosamine, piascledine, capsaicin within two weeks of baseline.
SUMMIT	Exclusion criteria: Kellgren-Lawrence grade 3 or 4 osteoarthritis
TIG/ACT	Exclusion criteria: Advanced osteoarthritis (as defined by Radiographic Atlas of Osteoarthritis, grade 2-3), taking specific osteoarthritis drugs, such as chondroitin sulfate, diacerein, n-glucosamine, piascledine, and capsaicin, within 2 weeks of the baseline visit

The effects of the heterogeneity are mixed;

- Comparing Spherox and VerMACI using COWISI and SUMMIT should disadvantage Spherox because of the baseline KOOS scores and defect sizes
- Comparing Spherox and VerMACI might disadvantage the latter because of the longer duration, if we extrapolate from TIG/ACT 5-year data which showed that ACI was less successful in defects with longer duration
- Comparing Spherox with both the other trials should disadvantage VerMACI and ChondoCelect because of the previous repair attempts

Transitivity assumption

The Co-Don submission does not discuss whether or not they assessed the transitivity assumption and whether it was violated. If the transitivity assumption is compromised or does not hold, the consistency assumption is also violated, leading to biased estimates in the network meta-analysis. The ERG examined the transitivity assumptions applicable to the NMA included in the CS.

The transitivity assumption does not hold if the distribution of population characteristics that are effect modifiers differ across the treatment comparisons of a network. Three such treatment effect modifiers in the Company's NMA are the KOOS score, the lesion size at baseline and previous repair attempts. The networks for the proportion of responders and failure rate include three RCTs of clinically diverse populations based on the KOOS score and lesion size at baseline, rendering the compared treatments in the networks not jointly randomizable. The uneven distribution of these effect modifiers across the network comparisons violates the transitivity assumption.

Another threat to transitivity assumption is the potential difference within the microfracture interventions as previously described, which means that these interventions may not be exactly considered as one node of microfracture.

Lastly, there was some variation on the definition of responders, one of the NMA outcomes, which means that the number of responders was not assessed consistently across studies. Failure rates were reported over different timescales (2 years for SUMMIT and COWISI, 3 years for TIG/ACT, though 2-year data for TIG/ACT were available).

Overall, owing to the violations on transitivity assumption, the validity of the estimate for the indirect comparisons is very questionable.

ERG comments

On page 78, there is a statement: "*The median RRs suggest that Spherox is associated with a higher number of responders when compared to MF".* This is not what was reported from the trial in Co-Don Table 30 – there were [redacted] responders for Spherox and MF respectively, and in the forest plot the RR is 0.9684. The text does note that the results are not statistically significant.

On page 80, there is a comment that TIG/ACT only published outcomes at three years. This is not entirely correct. Saris and colleagues[38] provide 2-year data (in the figures) for KOOS scores and treatment failures, showing a clear separation of KOOS scores and failure rates between ACI and MF arms by 24 months.

On page 83, table 38 shows differences in the MF KOOS results for the MF arms in COWISI and SUMMIT, with the statement that:

At the end of the 24th month, patients receiving Spherox and MACI report [redacted].

A more likely explanation is lesion size, which is much smaller in COWISI than SUMMIT (means of about 2.1 and 4.8 respectively). So we would expect much better MF results in COWISI.

Table 82 has a few unimportant errors. The studies by Clave et al[43] and Jones et al[44] were probably meant to be listed as exclusions. We note that Knutsen et al 2016[45] is listed as an inclusion, but is not in the NMA. Knutsen 2004[46] is listed as an exclusion but it could be argued that it is relevant, as an RCT of ACI versus MF.

3.7 Evidence from case series

The Co-Don submission reports that Chondrosphere has been used in Germany since 2004, and that more than 10,000 patients have been treated. Unfortunately this widespread use does not seem to have been accompanied by an equivalent amount of data collection. In the submission to the EMA, 11 studies were included, but all but one were "case studies, conference posters and study reports without detailed information of the conducted study". (CHMP 2017). Some were about ACI in the hip joint. Spherox has been used in knee, ankle, shoulder and hip.[47]

The ERG has identified some case series. Co-Don did not use these in their submission, except in a list in an appendix. Given that we have evidence from only one (as yet) short-duration RCT with an active comparator, we have looked at some case series to see what can be gleaned.

Quality assessments are provided in Appendix 1. Note that studies can be assessed as poor quality for two reasons;

- The study was of poor quality
- The study might have been good quality but insufficient details are provided to assess quality

Fickert et al 2012 [48]

This case series was assessed as fair quality. Fickert et al from Mannheim in Germany recruited 37 patients with isolated chondral defects in the knee, roughly half patellar and half femoral condyle. 13% had had previous attempts at repair. Duration of defects ranged from 2 months to 11 years, but analysis of results by duration under one year or over showed no difference in most outcomes, Tegner being the exception.

Implantation was by medial mini-arthrotomy with mean operation time 60 minutes. The authors noted the possibility of arthroscopic implantation.

Seven of the 37 had AEs, mainly local such as effusion and locking, but with one deep vein thrombosis (DVT) and pulmonary embolism. The patient who had the DVT and embolism was aged 46, and had a longer than usual (148 minutes) operation that included ACL reconstruction.

There were no important differences by defect site, leading Fickert et al to suggest that Spherox may be more effective in patellar defects than other forms of ACI.

Improvements in SF-36 are reported but no p values are given and the improvements, while definite, do not appear from the graph to be statistically significant.

One weakness of the study is that follow-up was only for 12 months, but longer follow-up was planned. However, we have found no further publications from Fickert and colleagues.

The lack of a control group is the main weakness. One strength is that the recruits may be more typical of routine practice than RCT recruits. Six had BMIs over 30 and several were over 50 years of age.

Siebold 2015 [49]

Siebold and colleagues from Heidelberg performed "second-look" arthroscopy on 57 cartilage lesions in 41 patients at a median of 10 months, mean 13 months (range 6 to 72 months) after arthroscopic spheroid implantation. No information is given on what proportion of all patients treated with spheroids had second-look arthroscopy, but all who did had another reason for arthroscopy (table 3 of paper) – none of the arthroscopies were done just to evaluate the cartilage repair. So this case series may not reflect the outcomes for the generality of Spherox patients. It is noted that 27 patients (66%) had ACI combined with other procedures, which is common, and understandable in the interests of patient care, but which does make interpretation of the benefits of ACI more difficult.

The ICRS Cartilage Repair Assessment grading, based on visual inspection and probing, was reported to be normal in 12 lesions (21%), nearly normal in 40 (70%) and abnormal in 5. Clinical follow-up data (KOOS etc) was not available in 24%, but in any case, baseline pre-operation data were not provided. None of the patients reported by Siebold et al had had previous repair attempts such as microfracture.

Maiotti 2012 [50]

This study was available only as an abstract with sparse detail making quality assessment difficult. It reports on only 23 patients, of whom only three had follow-up biopsies. One useful item was that the spheroids were all implanted arthroscopically.

Roessing 2010 [51]

This is available only as an abstract from an ICRS meeting, so details are sparse, and we have not attempted quality assessment. 42 patients had spheroids implanted arthroscopically. The aim of the study was to show that spheroids could be implanted arthroscopically, in which it succeeded. Follow-up was for 2 years, during which time no failures requiring further surgery occurred, and symptoms improved (no figures given). The patients in Roessing may include some from the unpublished Co-Don document cod RS1 SR 2015, which had 19 patients.

Schreyer 2010 [52]

Schreyer and colleagues from Darmstadt in Germany compared three ways of implanting Co-Don chondrocytes: by ACI-P (40 patients 1998 to 2004), and as spheroids (2005-2009) by arthrotomy (15) or arthroscopically (16). They concluded that uncapped implantation was as good as with ACI-P.

Other studies

Some other data were supplied to the EMA and reported in the CHMP assessment report 2017. These included an unpublished case series by Zinser in Dinslaken, Germany, in which before and after improvement in the IKDC from 39 to 61 points was reported. However only 36 of 90 patients treated agreed to the analysis, raising questions of selection bias. Data from three pilot studies, including six patients treated by Dr Schreyer in Darmstadt, 26 from Dr Ruhnua in Buer and 10 from Dr Baum in Gundelfinger, are summarized in a book chapter by Libero and colleagues [47] which also provides a good account of the pre-clinical research on spheroids. These three pilots all report useful improvements in clinical scores, but their usefulness is limited, because of lack of control groups or even natural history studies. The chapter states that implantation was by "mini-arthroscopy", but we assume this means mini-arthrotomy.

In summary, these case series provide evidence of before and after improvement, and that Spherox can be implanted arthroscopically. Without comparators, their usefulness is limited.

3.8 Conclusion and discussion

The ERG's main conclusions at this stage are;

1. COWISI was a good quality trial, though blinding of intervention was impractical, duration of patient follow-up is as yet only two years, and it included patients with defects smaller (<2cm^2) than NICE currently approves for ACI

2. Spherox is clinically effective in treatment of chondral defects, and the improvement lasts for at least four years.

3. However, the comparative effectiveness is an issue. The evidence presented does not show [redacted]. This is perhaps not surprising, since MF is effective in the short-term, in smaller defects. So with longer follow-up, we would expect the benefits of MF to wane. We note that in the comparator trials, TIG/ACT and SUMMIT, ACI was showing an advantage over MF by 2 years, but these differed in some ways from COWISI.
4. We doubt whether it was appropriate to do the NMA given the heterogeneity. We do not regard the results of the NMA as robust, and insufficient to support the cost-effectiveness analysis.

If these conclusions are accepted, no positive results on clinical effectiveness are available to feed into the modelling, and we might stop here. However, the Appraisal Committee may take a more sympathetic view, so in the next section we provide a critique of the Co-Don cost-effectiveness analysis.

4 Cost-effectiveness

4.1 ERG comment on manufacturer's review of cost-effectiveness evidence

In the main, the company literature review provides a good summary of the available papers and their central cost effectiveness estimates. More could have been made of the scenario analyses of Mistry et al[42] particularly the scenario analyses around the effects of previous interventions and the effects of severity. It would also have been much improved if the company had summarised the evolving debate, cost effectiveness estimates and conclusions of the ACI MTA [TA477].[53]

4.2 Summary and critique of manufacturer's submitted economic evaluation

4.2.1 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the de novo economic evaluation match the reference case**
Comparator(s)	The scope specifies: • Microfracture • ACI • Debridement • Mosaicplasty • BSC	The submission considers: • Microfracture (MF) • ACI: Spherox • ACI: ChondroCelect • ACI: MACI These are only considered in sequences where a 2nd repair is possible: • MF->MF • MF->ACI • ACI->MF • ACI->ACI Where the 1st ACI is followed by a 2nd ACI, the 2nd ACI is assumed to be the same as the 1st ACI.
Patient group	As per NICE scope. "*People with articular cartilage defects*"	The submission only considers knee repair. This is in line with the SmPC and the recent ACI assessment [TA477].

		The pivotal trial was limited to defects of between 1cm^2 and 4cm^2. The SmPC permits treatment of defects up to 10cm^2. This complicates the NMA, which is further complicated by the proportions of patients having had a previous repair differing between the trials. The recent ACI assessment [TA477] has approved ACI for defects of more than 2cm^2, in part due to a consensus statement by a group of experts.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost utility.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. Lifetime.
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review and NMA are undertaken.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. The quality of life values for 1st and 2nd repairs are taken from and are in line with those of TA477. TA477 derived values from Gerlier et al [54] who[1] analyse the TIG/ACT trial 5 year follow-up SF-36 data mapped to the QoL using the Brazier et al [55] algorithm. The quality of life values for knee repairs are also taken from

[1] Sponsored by TiGenix NV, provider of ChondroCelect

		TA477, but are not entirely aligned with it.
Benefit valuation	Time-trade off or standard gamble	Yes. Standard gamble.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. 611 members of the UK general public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes. But the clinical effectiveness estimates are varied independently.
Sensitivity analysis		A reasonable range of sensitivity analyses are conducted.

4.2.2 Model structure

A markov model with an annual cycle is developed based on the recent model of Mistry et al [42]. While the model structure is similar to that of Mistry et al, the transition probabilities differ quite considerably from it. In the opinion of the ERG the presentation of the model and the transition probabilities of tables 47 and 48 of the submission does not accurately or transparently present the implementation of the model. Section 3.3.3 of the submission should be read alongside the detail of section 5.2.6 on treatment effectiveness and extrapolation below.

The model compares 10 sequences, each sequence having two treatments or repairs. Up to the age of 55 only the two repairs of the sequence may be received. Thereafter patients may receive knee replacements.

Model structure to the age of 55

All patients receive the 1st repair of the sequence during the 1st cycle of the model. These patients can move into one of three health states[2].

- Success
- No further repair (NFR)
- 2nd repair

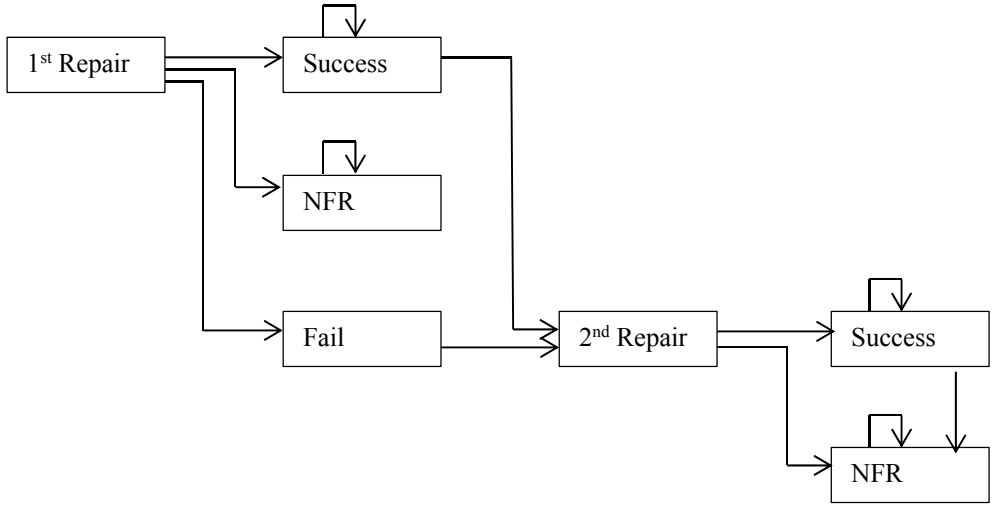
Subsequent to the 1st cycle those who were a success either remain a success or move to 2nd repair. All those in NFR remain in NFR.

The patients who receive the 2nd repair of the sequence can move into one of two health states.

- Success
- No further repair (NFR)

Those who were a success either remain a success or move to NFR. All those in NFR remain in NFR.

Figure 2 Model structure to age 55



The above is a slight simplification. Both the 1st repair and 2nd repair successes are divided into 5 health states: four annual tunnel health states of success for years 1 to 4 after the repair and a fifth health state of success in years 5+ after the repair. This is in line with Mistry et al. It enables quality of life values specific to the duration of success, years 1, 2, 3, 4 and 5+, to be applied. These differ between:

- ACI repairs and microfracture repairs
- 2nd ACI repairs after a 1st microfracture repair and 2nd ACI repairs after a 1st ACI repair

[2] Death from all-cause mortality is possible from all health states but is largely ignored in this description for sake of simplicity. The 1st knee replacement increases the probability of death in the year of operation by 0.35%, and subsequent knee replacements by1.10%.

A key difference between the company model structure and that of Mistry et al is that there is no possibility of 1st repair successes losing the benefits of success and transitioning into the NFR health state. In the company model 1st repair successes can only transition to 2nd repairs.

Model structure subsequent to age 55

From the age of 55 the model structure is augmented by a knee replacement (KR) module. There is a common annual 1.01% probability of receiving a 1st KR for patients who are in the 1st repair success, the 1st repair NFR, the 2nd repair success and the 2nd repair NFR health states. Those receiving a 1st KR can move into one of three health states:

- Success
- No further repair (NFR)
- Subsequent KR

Subsequent to the 1st KR those who were a success either remain a success, move to NFR or receive a subsequent knee replacement. Note that this NFR health state differs from the NFR health state of those moving directly from their 1st KR to NFR without success and is associated with a different quality of life. Those in NFR remain in NFR.

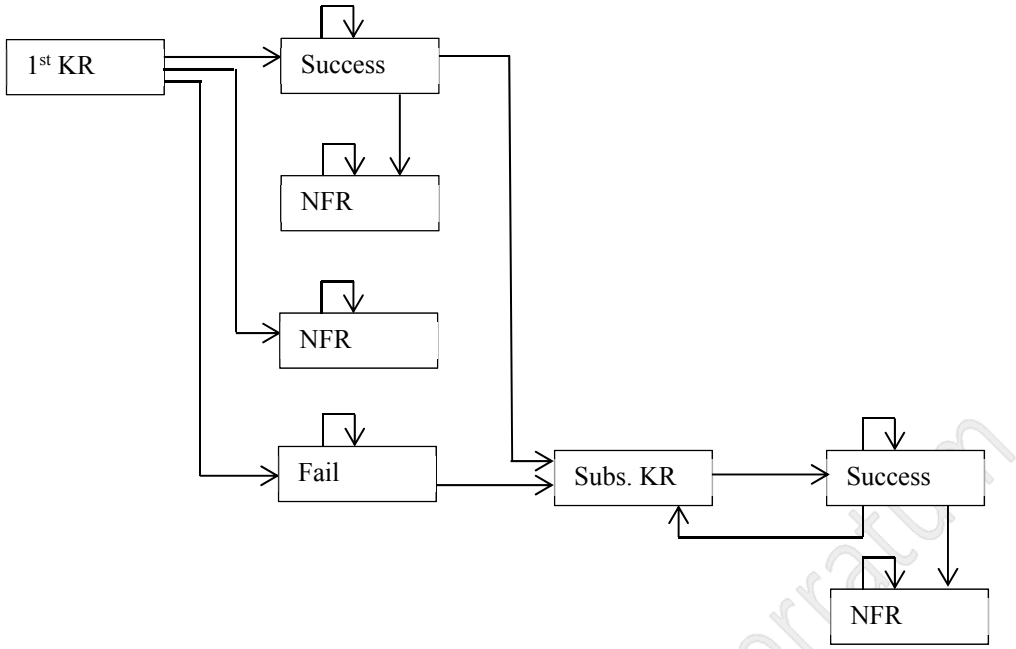
Those receiving a subsequent knee replacement can move into one of two health states.

- Success
- No further repair (NFR)

Those who were a success can either remain a success, move into NFR or receive a subsequent KR. The feedback loop between success and subsequent KR means that there is no limit on how many KRs a patient may receive. Those in NFR remain in NFR.

For the 1st knee replacement there is a 50:50 balance between total knee replacement (TKR) and partial knee replacement (PKR). All subsequent knee replacements are TKRs. This complicates the implementation of the KR module within the company electronic model

Figure 3 Knee replacement module from age 55



4.2.3 Population

The patient population reflects the baseline characteristics of the Phase III trial with a mean age at baseline of 34 years and 60% male.

4.2.4 Interventions and comparators

There are four main interventions:

- Microfracture (MF)
- Spherox (SPHX)
- MACI (MACI)
- ChondroCelect (CC)

All of these interventions are modelled as being part of a possible sequence of two repairs. The 1st treatment is applied to all patients. The 2nd treatment is applied to those requiring repairs after having received the 1st treatment. The 10 sequences that are compared are:

- Microfracture followed by another treatment:
    - MF->MF
    - MF->SPHX
    - MF->MACI
    - MF->CC

- Each ACI followed by microfracture:
    - SPHX->MF
    - MACI->MF
    - CC->MF
- Each ACI followed by itself:
    - SPHX->SPHX
    - MACI->MACI
    - CC->CC

4.2.5 Perspective, time horizon and discounting

The time horizon is 67 years, i.e. to 100 years of age, which is effectively a lifetime horizon. The perspective and discounting are as per the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The company submission contains many errors. As outlined in section 5.4 the ERG has revised all the clinical inputs to the model derived from the trials and the company NMA. The company accepts that many revisions are required. But it has not documented its new method, suggests revised values that differ from those of the ERG and has not provided a coherent set of responses and additional analyses. In the light of this much of the original submission is irrelevant. The detail of the submission is presented below for completeness and to explain the ERG critique and the ERG changes to the company model. Most readers may wish to move forward to section 5.2.7 on quality of life.

Treatment effectiveness: Response rates and probabilities of remaining a success

During the 1st annual cycle of the model the two year probabilities of response, P_2, are applied to the 1st repairs. In effect the 1st cycle of the model is two years rather than one year, though the QALY and cost calculations do not particularly take this into account.

For instance, the 1st cycle applies the 81% probability of response for Spherox 1st repairs. The probabilities of response for the other comparator treatments are derived by applying the relative risks of the NMA to the Spherox response rates.

The company submission and the clinical effectiveness section raise serious issues around the NMA and its validity. If the NMA is invalid it may still be possible to consider a head to head of Spherox with microfracture. This is complicated by the estimated benefits of Spherox over microfracture not

arising from the clinical effectiveness estimates of the trial but stemming almost entirely from the assumption that all microfracture fails at 5 years.

The response rates are calculated as rate = $-\ln(1-P_2)*RR$, with these rates being back transformed along the lines of 1-exp(-1*rate) to yield the two year probability of response for the comparator. This is equivalent to estimating the two year probability of response for the comparator as $1-(1-P_2)^{RR}$, or defining the two year non-responder or failure rate as $F_2 = (1-P_2)$ is more simply $1-F_2^{RR}$.

Table 10 Two year probabilities of response for 1st repairs

	SPHX	CC	MACI	MF
Spherox 2yr probability of response $Sp(P_2)$	[redacted]			
Relative risk (RR)	1.000	1.209	1.223	0.968
1st repair 2yr probability of response $P_2 = 1-(1-Sp(P_2))^{RR}$	[redacted]	86.57%	86.88%	79.98%

To be able to outline what the company has applied for the treatment effectiveness of 2nd repairs and the ongoing probabilities of failure rates requires a small digression on the conversion of two year probabilities to annual probabilities[3].

If the two year probability of response is P_2 then for modelling purposes it is possible to take the square root of this to yield an annual probability of $P_1 = (P_2)^{½}$. While slightly curious in the current context, this annual probability of P_1 could then be applied during two cycles and the cumulative probability would be $P_1 * P_{1=} P_2$ and the correct proportion of responders would be modelled as occurring at the end of the 2nd year.

As an example the 2 year probability of response for Spherox is [redacted]. The square root of [redacted] is [redacted] which is the company estimate of the annual probability of response for Spherox as a 2nd repair. But the company model only applies this [redacted] annual probability once for 2nd repairs and does not compound it over two years to arrive at the [redacted] two year response rate. The response rates for 2nd repairs are consequently modelled as being much higher than the response rates for 1st repairs.

A similar logic can be applied if the probabilities of failure are to be modelled rather than probabilities of response, where by definition $F_1 = (1-P_1)$. By substitution $F_1 = 1-(P_2)^{½}$, and since $F_2 = (1-P_2)$ implies that $P_2 = (1-F_2)$ this in turn implies that $F_1 = 1-(1-F_2)^{½}$.

[3] This is simplified to only consider probabilities. The company implementation converts 2 year probabilities to annual rates along the lines of $r=-\ln(1-P_2)/2$ and from there to annual probabilities by $P_1=1-e^{-r}$. Substitution causes the exponentiation of the logarithm to disappear resulting in $P_1=1-(1-P_2)^{½}$.

The company applies the formula for failures to the two year probability of response P_2 rather than the two year failure rate F_2. For instance, applying the formula for failures to the [redacted] two year probability of response for Spherox yields a probability of [redacted] = 56.41%. The company takes this to be the annual probability of a successful Spherox repair failing and the patient moving into the No Further Repair (NFR) health state. This annual probability is not limited to being applied once, but is applied every cycle of the model to those with a successful Spherox 2nd repair.

This is most easily seen in table 48 on page 114 of the submission in the Spherox followed by Spherox transition probability matrix entry of 0.5641 for the probability of failing and moving from a successful 2nd repair to NFR. The residual of 0.4359 is the annual probability of remaining a successful 2nd repair.

Table 48 of the Co-Don submission suggests that a similar probability of 1st repair successes failing and moving into the NFR health state is applied. The 0.5500 entry of table 48 is based upon the 0.5641 probability, adjusted for the 0.0063 probability of 1st repair successes failing and receiving a 2nd repair. In the opinion of the ERG there is no probability of 1st repair successes moving into the NFR health state. The only means of exiting the 1st repair successes health state[4] is via a 2nd repair and for those age 55+ via a 1st KR.

This results in the following estimates for the probabilities of response from 2nd repairs and the annual probabilities successes from 2nd repairs failing and moving into the NFR health state[5]. These are independent of the type of 1st repair.

Table 11 Probabilities of 2nd repair responses and 2nd response successes to NFR

	SPHX	CC	MACI	MF
Spherox 2yr probability of response $Sp(P_2)$	[redacted]			
Relative risk (RR)	1.000	1.209	1.223	0.968
1st repair 2yr probability of response $P_2 = 1-(1-Sp(P_2))^{RR}$	[redacted]	86.57%	86.88%	79.98%
2nd repair probability of response = $P_2^{½}$	[redacted]	93.04%	93.21%	89.43%
Annual probability of 2nd success failing to NFR = $1-(1- P_2)^{½}$	56.41%	63.36%	63.78%	55.25%

Probabilities of a 2nd repair

The probabilities of a 2nd repair differ between the 1st cycle of the model and subsequent model cycles. For the 1st cycle of the model for both Spherox and MACI these are assumed to be zero. For

[4] Ignoring death.

[5] Though as already outlined the annual probabilities of success from 1st repairs moving into the NFR health state

the 1st cycle of the model for ChondroCelect and microfracture these are derived from the NMA input of a probability of [redacted] for Spherox coupled with the NMA relative risks of 2.032 for ChondroCelect and 6.979 for microfracture. As for the probabilities of response the relative risks are applied to the rate for Spherox and then back transformed to probabilities, resulting in a 2 year probability of failure of 1.01% for ChondroCelect and 3.44% for microfracture.
For subsequent cycles of the model, those who are an ACI success are assumed to have a 2 yearly probability of a 2nd repair of 1.25% as taken from Mistry et al. This is converted to an annual probability of 0.63%.

For subsequent cycles of the model, those who are a microfracture success are assumed to have a 2 yearly probability of a 2nd repair of 3.44% / 2 = 1.72%. This is converted to an annual probability of 0.86%. In effect the 2 year 3.44% probability derived from the NMA is quartered.

Knee replacement module
From the age of 55 all those remaining with a successful repair or having failed and fallen into the NFR health state have a common annual probability of being given a 1st knee replacement of 1.01%. There is a 50:50 balance between total knee replacements and partial knee replacements. Those who have had a knee replacement also have a common probability of 1.01% of having another knee replacement, all of which are total knee replacements.

Based upon Mistry et al 1st total knee replacements are associated with an increased probability of death of 0.7%, and 2nd total knee replacements 1.1%.

1st knee replacements have a 0.20% annual probability of failing and receiving no further treatment and a 0.58% annual probability of failing and receiving a subsequent knee replacement. The remainder have a successful 1st knee replacement.
Subsequent knee replacements have a 2.09% annual probability of failing and receiving no further treatment. The remainder have a successful subsequent knee replacement.

Those with a successful knee replacement, whether a 1st or a subsequent knee replacement, have a 1.62% annual probability of failing and receiving no further treatment and a 1.08% annual probability of failing and receiving a subsequent knee replacement.

4.2.7 Health related quality of life

Most of the quality of life values within the submission are taken from Mistry et al. Mistry et al derived their quality of life values for repair health states from Gerlier et al [54], and their quality of life values for knee replacement health states from Dong and Buxton[56], Gerlier et al[54] and Jansson and

Granath[57]. Gerlier et al mapped to the SF-36 data collected during the 5 year follow-up of the TIG/ACT trial to quality of life values using the Brazier et al[55]SF-36 to SF-6D to quality of life mapping function.

There are two key assumptions.

- In common with Mistry et al the company assumes that for microfracture all successes fail completely at year 5. This causes them to fall back to the baseline quality of life value of 0.654. The AC of the ACI MTA [TA477] requested a scenario analysis that assumes that the quality of life is maintained at 0.817. The company also provides this scenario analysis.
- For those receiving an ACI as a 2nd repair after a 1st repair of microfracture their 2nd repair deteriorates at year 4. This causes their quality of life to be the midpoint between the 1st year quality of life value of 0.760 and the quality of life of success of 0.817: 0.789. This assumption makes it less likely that reserving ACI to be only an option as a 2nd repair will be cost effective.

Table 12 Quality of life values for successful repairs

	1st repair		2nd repair		
	ACI	MF	ACI post ACI	ACI post 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

In addition to the above quality of life values those moving into the failure and NFR health state after their repair have a quality of life value of 0.691. Those requiring a 2nd repair receive a quality of life value of 0.654 for that cycle.

For knee replacements the quality of life values are as follows.

Table 13 Quality of life values for knee replacements

Health state	QoL
1st KR	0.615
Subs KR	0.557
Success	0.780
NFR from 1st KR	0.691
NFR from 1st KR success	0.557
NFR from 2nd KR	0.557
NFR from 2nd KR success	0.557

4.2.8 Resources and costs

The resource use and many of the unit costs within the submission are taken from Mistry et al. With the exception of cell costs, the unit costs taken from Mistry et al are in 2012/13 prices and so are inflated by 3.4% to be in 2015-16 prices. These costs in Mistry et al are sourced from Clar et al 2005[58] and inflated from 2013-12 prices.

A company assumption is that Spherox implantation is done arthroscopically so requires a less invasive and shorter implantation procedure than other ACIs and so only incurs costs of £734 for both harvesting and implantation. The balance between total knee replacements and partial knee replacements is assumed to be 50:50 for 1st knee replacements, with all subsequent knee replacements being total knee replacements.

Unit costs of visits are taken from NHS reference costs. Unit costs of knee replacements are taken from the 2016-17 National Prices and Tariff.

Table 14 Unit costs

	Cost	Source
Harvesting	£734	Mistry et al, Arthroscopy, Table 22, inflated
Implanting SPHX	£734	Mistry et al, Arthroscopy, Table 22, inflated
Implanting CC and MACI	£1,065	Mistry et al, Arthrotomy, Table 22, inflated
Procedure MF	£3,122	Mistry et al, Procedure, Table 22, inflated
1st knee replacement	£5,556	2015-16 National Tariff
2nd knee replacement	£13,396	Mistry et al, 2nd TKR, Table 22, inflated
Outpatient visit	£121	Ref Cost: WF01A: OP: NA: FF: CL
Rehabilitation visit	£345	Ref Cost: REHBL2: rehabilitation for joint replacement

This, coupled with the cell costs and the visit and rehabilitation schedule of Mistry et al, results in the following total costs.

Table 15 Total costs of procedures

	SPHR	CHON	MACI	MFRC	1st KR	Subs KR
Cost of cells	£10,000	£16,000	£16,000	..	..	..
Harvesting	£734	£734	£734	..	..	..
Implantation	£734	£1,065	£1,065	..	..	..
Procedure	..	..	..	£3,122	£5,566	£13,397
Procedure cost	£11,468	£17,799	£17,799	£3,122	£5,566	£13,397
OP	6	6	6	3	2	2
Rehabilitation	3	3	3	3	0	0

Total Cost	£13,226	£19,556	£19,556	£4,518	£5,807	£13,638

4.2.9 Cost effectiveness results

As already outlined, the company accepts that the methods of its submission are incorrect. Following further clarification the company has submitted a deterministic set of results. In brief among the non-dominated sequences these are as follows. (Note that second procedures are only if required.)

Table 16 Revised company cost effectiveness results

	Cost	QALYs	Δ Cost	ΔQALYs	ICER
MF->MF	£5,762	15.878			
SPHX->MF	£14,174	17.955	8,412	2.077	£4,051
SPHX->SPHX	£14,993	18.000	819	0.045	£18,137
MACI->MACI	£22,312	18.395	7,319	0.395	£18,523

A key point to note in the above is that the cost effectiveness estimate for SPHX->SPHX compared to SPHX->MF of £18,137 per QALY is only slightly below the implied cost effectiveness estimate of MACI->MACI compared to SPHX->MF of £18,483 per QALY. It will only take a small increase in the effectiveness of MACI for SPHX->SPHX to be extendedly dominated by MACI->MACI. The ERG revised estimates suggest such an increase compared to the company revised estimates, as outlined in greater detail in section 5.3.4 below.

The revised company deterministic results are not accompanied by a revised electronic model, probabilistic modelling or sensitivity analyses. In the light of this the results of the original submission are presented below for completeness. But other than to inform the examination of the original company sensitivity analyses they are largely irrelevant.

Original submission results

The company base case deterministic results are as follows.

Table 17 Company deterministic base case results

	Cost	QALYs	Δ Cost	Δ QALY	ICER
MF->MF	£5,763	15.851	..	..	..
MF->SPHX	£7,156	15.851	..	..	Ext. Dom.
MF->CC	£8,168	15.849	..	..	Dominated
MF->MACI	£8,168	15.849	..	..	Dominated
SPHX->MF	£14,182	17.971	£8,419	2.120	£3,971
SPHX->SPHX	£15,017	17.972	..	..	Ext. Dom.
MACI->MF	£20,544	18.117	£6,362	0.146	£43,676

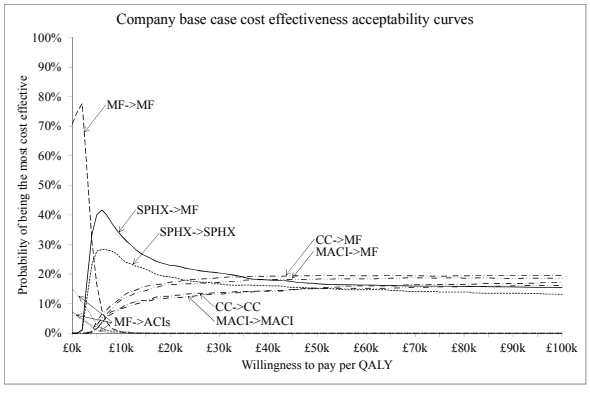
CC->MF	£20,588	18.110	..	..	Dominated
MACI->MACI	£22,091	18.116	..	..	Dominated
CC->CC	£22,283	18.109	..	..	Dominated

The central estimates of the company probabilistic modelling over 1,000 iterations are broadly similar to the deterministic. The main change is that the cost effectiveness of MACI->MF compared to SPHX->MF falls to £33,206 per QALY. MACI->MF also no longer dominates MACI-MACI, though the cost effectiveness of MACI->MACI remains very poor compared to MACI->MF.

Table 18 Company probabilistic base case results

						Pr(c/e) with WTP	
	Cost	QALYs	Δ Cost	Δ QALY	ICER	@£20k	@£30k
MF->MF	£5,601	15.827	..	..	..	0%	0%
MF->SPHX	£6,827	15.833	..	..	Ext. Dom.	0%	0%
MF->CC	£7,727	15.831	..	..	Dominated	0%	0%
MF->MACI	£7,793	15.828	..	..	Dominated	0%	0%
SPHX->MF	£14,029	18.001	£8,469	2.134	£3,959	18%	20%
SPHX->SPHX	£14,783	17.994	..	..	Ext. Dom.	19%	17%
MACI->MF	£20,392	18.109	£6,348	0.191	£33,206	19%	17%
CC->MF	£20,444	18.155	..	..	Dominated	15%	19%
MACI->MACI	£21,687	18.110	£1,266	0.003	£477k	14%	13%
CC->CC	£21,996	18.148	..	..	Dominated	14%	14%

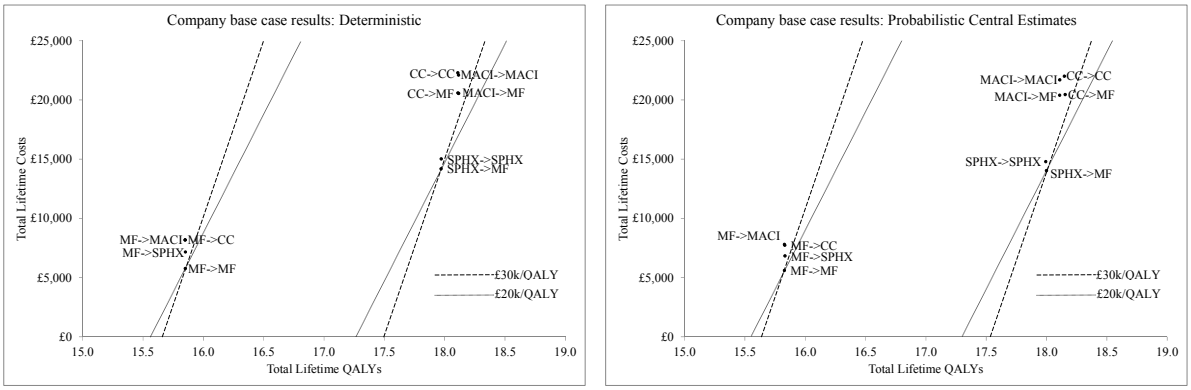
Figure 4 Company base case CEAC



There is an argument for considering the set of sequences with microfracture as the 1st repair separately from the set of sequences with a form of ACI as the 1st repair. This is most simply achieved graphically on the cost effectiveness plane. Since the results suggest two possible sequences as bases, MF->MF and SPHX->MF, total amounts rather net amounts are presented in what follows. This does

not affect the relative position of the sequences, and cost effectiveness lines for £20k/QALY and £30k/QALY can be drawn using the two possible bases as the "origin".

Figure 5 ***Company base case results in the cost effectiveness plane***



There is little probability of a microfracture 1st repair followed by any of the ACIs as 2nd repairs being cost effective at any willingness to pay values.

The likelihood of an ACI as 1st repair followed by itself as 2nd repair being the most cost effective is always less than that of the same ACI as 1st repair followed by microfracture as 2nd repair.

4.2.10 Sensitivity analyses

As outlined at the start of section 5.2.9 the company accepts that there are major errors in its submission. It has provided a revised deterministic base case as summarised at the start of section 5.2.9. It has not provided probabilistic estimates or sensitivity analyses around this. The sensitivity analyses of the original submission are presented below. These are still of some use in showing the structural uncertainty around the model.

Original submission sensitivity analyses

The company presents a range of sensitivity analyses for SPHX->MF compared to MF->MF. This is presented as the effect upon the net monetary benefits (NMB) valued at a willingness to pay of £20k per QALY[6]. This appears to vary a number of inputs by an arbitrary ±20% and concludes that the NMB at £20k per QALY for SPHX->MF compared to MF->MF remains positive throughout. Results are most sensitive to varying the quality of life values for years 5+ that are applied to Spherox and to microfracture.

A number of deterministic scenario analyses are also presented by the company. These broadly preserve the ordering of the sequences and the patterns of dominance and extended dominance. Their

[6] For full details see Table 64 page 144 and Figure 18 page 145 of the company submission.

main effect is to alter the deterministic base case cost effectiveness estimate for SPHX->MF compared to MF->MF and for MACI->MF compared to SPHX->MF.

Table 19 Company scenario analyses

Sequence	SPHX->MF	MACI->MF
Comparator	MF->MF	SPHX->MF
Base case ICER	£3,971	£43,676
SA01: 5 year time horizon	£75,395	£206k
SA02: 15 year time horizon	£8,497	£78,218
SA03: All 1st KR are TKR	£3,971	£43,676
SA04: All 1st KR are PKR	£3,971	£43,676
SA05: QoL NFR = QoL Failure = 0.654	£4,008	£32,838
SA06: QoL Failure = QoL Success = 0.817	£3,991	£43,333
SA07: QoL Failure = QoL Success = 0.746 (midpoint)	£3,982	£43,481
SA08: QoL MF Yr5+ = QoL ACI Yr5+ = 0.817	Ext. Dominated	£62,927*
SA09: QoL prior to 2nd KR = QoL prior to 1st KR = 0.615	£3,971	£43,676
SA10: Spherox implantation same as other ACIs = £1,065	£4,127	£41,405
SA11: Spherox same responder rate as microfracture	£3,936	£43,680
SA12: Spherox same failure rate as microfracture	£4,061	£43,676
* ICER for MACI->MF vs MF->MF due to SPHX->MF being Ext. Dominated		

The main result of interest is that if success with microfracture persists SPHX->MF is extended dominated and the cost effectiveness of MACI->MF compared to MF->MF is poor.

No subgroup analyses are presented.

4.2.11 Model validation and face validity check

Original model face validation

The company model estimates that MF->SPHX results in more QALYs than MF->MACI and MF->CC. 2nd repairs with MACI and ChondroCelect are estimated to have higher probabilities of response than 2nd repairs with Spherox. This raises questions about the face validity of the model and in particular the modelling of 2nd repairs.

The company model also estimates that MACI->MF results in more QALYs than MACI->MACI, and that CC-> MF results in more QALYs than CC->CC. 2nd repairs with MACI and ChondroCelect are estimated to have higher probabilities of response than 2nd repairs with microfracture. This again raises questions about the face validity of the model and in particular the modelling of 2nd repairs.

The AC for TA477 expressed some scepticism that all microfracture repair successes would fail after 5 years. This is the main source of the QALY gain for Spherox over microfracture. The company has addressed this with a scenario analysis which applies the same quality of life value for microfracture repair successes for years 5+ as for year 1-4. This has a large impact upon results. In the opinion of the ERG it is such an important assumption that it warrants full exploration. The company model structure only permits this assumption to be turned on or turned off. As a consequence, the ERG will present a full set of analyses with the assumption that all microfracture repairs fail after 5 years and without it.

ERG revised model face validation

The main validation work that can be conducted is to revise the model inputs to be broadly in line with those of the various reports that underlie the ACI MTA [TA477] and check if the model outputs are broadly in line with those of the ACI MTA reports.

The 1st AG report clinical effectiveness estimates of response for ACI of 83% and microfracture of 62% are aligned with those of the TIG/ACT trial and the company model can be revised to apply these estimates.

The 1st AG report clinical effectiveness estimates for 1st repair successes failing and requiring a 2nd repair are 0.63% for ACI and 1.61% for microfracture. These compare to 0.63% for ACI and 3.44% for microfracture in the company model.

The quality of life values and cost inputs of the 1st AG report and ACI monograph are broadly in line with those of the company model. Only a value in the knee replacement module has to be revised and the ACI cost set to £16,000 to largely align the company model inputs with those of the 1st AG report.

Table 20 Model validation against AG reports ACI MTA

	Company model		1st AG report (table 16)		3rd AG report (table 2)	
	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	

The company model cost estimates are reasonable aligned with those of the 1st AG report. The total QALYs for ACI->ACI are also broadly aligned. But the total QALYs for MF->ACI are considerably less and result in the net QALY gain more than doubling to 2.131 QALYs. As a consequence the cost effectiveness estimate of the company model is around half that of the 1st AG report.

The ERG has not managed to identify why there is this discrepancy. A possible source is the different model structure with 1st repair successes only being able to transition to a 2nd repair and not to lose the benefits and move into the NFR health state. But the ERG would anticipate this further reducing the total QALY estimates in both arms, albeit by more in the ACI arm than in the microfracture arm.

During the course of the ACI MTA the AC requested longer term time to event data on loss of success be incorporated into the AG modelling, with the 3rd AG report reflecting this. This also revised the costs of harvesting to £870 and the costs of implantation to £2,396. The company model does not reflect the publicly available time to event data. But the AG incorporation of this data appears to reduce the net QALY gain from ACI over microfracture.

4.3 ERG cross check and critique

4.3.1 Base case results

The company model is constructed in an extremely convoluted manner, with a number of odd constructs and a number of dead ends in terms of inputs and TPMs not feeding through to the actual model. This is in part the reason for table 48 of the submission having limited relevance to the actual model inputs. In section 4.4 the ERG makes extensive changes to the company model and the base case results change markedly.

The ERG has rebuilt the company deterministic model using the same assumptions as the company and gets near complete agreement with the company model results.

Table 21 ERG rebuild vs company model: Company base case

	ERG Rebuild		Company model	
	QALY	Cost	QALY	Cost
MF->MF	15.851	£5,765	15.851	£5,763
MF->SPHX	15.851	£7,157	15.851	£7,156
MF->CC	15.849	£8,170	15.849	£8,168

MF->MACI	15.849	£8,170	15.849	£8,168
SPHX->MF	17.971	£14,184	17.971	£14,182
SPHX->SPHX	17.972	£15,018	17.972	£15,017
MACI->MF	18.117	£20,546	18.117	£20,544
CC->MF	18.110	£20,590	18.110	£20,588
MACI->MACI	18.116	£22,092	18.116	£22,091
CC->CC	18.109	£22,283	18.109	£22,283

4.3.2 Data Inputs: Correspondence between written submission and sources cited

Clinical effectiveness

A variety of clinical inputs are derived from Mistry et al. The following elements cross check:

- The 1.25% 2 yearly ongoing probability of moving from a successful ACI 1st repair to a 2nd repair.
- All the probabilities associated with knee replacement.

There is slight divergence between:

- The 3.44% 2 year probability of moving from a successful microfracture 1st repair to a 2nd repair of the model which implies an annual probability of 1.73%, and the 1.61% estimate Mistry et al derive from Saris et al.[39]

Quality of life

The quality of life values applied by the company for repairs cross check with those of Mistry et al, including the assumptions that:

- quality of life among microfracture 1st repair and 2nd repair successes for years 5+ after the repair declines to 0.654, and
- quality of life among ACI 2nd repair successes after a microfracture 1st repair for year 4 and years 5+ after repair declines to 0.789.

The quality of life values applied by the company for knee replacements do not entirely cross check with those of Mistry et al. In Mistry et al those with no further repair (NFR) had a common quality of life value of 0.691. The company revises these for most of the NFR health states to 0.557. This worsens the cost effectiveness of sequences that result in more knee replacements.

Table 22 Knee replacement quality of life values cross check

	QoL	
Health state	Company	Mistry et al
1st KR	0.615	0.615
Subs KR	0.557	0.557
Success	0.780	0.780
NFR from 1st KR	0.691	0.691
NFR from 1st KR success	0.557	0.691
NFR from 2nd KR	0.557	0.691
NFR from 2nd KR success	0.557	0.691

The ERG will apply the quality of life values of Mistry et al.

Resource use and unit costs

The resource use in terms of outpatient visits and rehabilitation visits cross check with Mistry et al. The unit costs sourced from Mistry et al table 22 cross check when a 3.4% inflation uplift is taken into account

The HRG codes for OP visits and rehabilitation visits cross check with those of Mistry et al.

- The unit cost of £121 for OP paediatric trauma and orthopaedics has been applied, incorrectly. The unit cost of OP trauma and orthopaedics of £110 should be applied.
- The unit cost of rehabilitation cross checks.

The 2012-13 HRG code of HB21C major knee procedure: non-trauma, cat 2, no CC appears to have been superseded in the 2015-16 reference cost HRG codes. The 2015-16 reference cost HRG codes with the closest description to these are HN23A to HN23D for Major Knee Procedures for Non-Trauma, 19 years and over with different CC scores. These are as below for elective inpatients.

Table 23 Major Knee Procedures: 2015-16 Reference costs

HRG	CC Score	FCEs	Mean cost	Mean LoS
For Non-Trauma				
HN23A	4+	330	£5,746	6.0
HN23B	2-3	1025	£4,118	2.7
HN23C	0-1	7318	£3,587	1.4

The company does not use NHS reference costs, but unusually chooses to use the 2016-17 National Prices and Tariff of £5,566. This cross checks with Annex A: HRG code HB21C: Major Knee Procedures for Non-Trauma, Category 2, without CC. It is also broadly in line with the uninflated cost of knee replacement of £5,676 of Mistry et al. The model is not sensitive to the cost of knee replacement.

The cell costs of £16,000 for MACI and ChondroCelect cross check with Mistry et al table 22. However, the TA477 AG report noted that CIC discounts were available to these costs and over the course of the assessment undertook a range of scenario analyses that varied the cell costs to £16,000, £12,000, £8,000 and £6,000.

For the ACI MTA [TA477] OsCell initially reported cell costs of around £4,100 but the AC was concerned that this did not account for overheads. OsCell supplied another costing of £6,000 inclusive of overheads, and £9266 including both procedures.

Many of these costs have been superseded by the FAD of the MTA of ACI [TA477] which preferred:

- Harvesting costs of £870 (HRG HB25F)
- Implantation costs of £2,396 (HRG HB22C)
- OsCell cell costs of £6,000 inclusive of overheads, though the FAD suggests that this may still be an underestimate due to not fully accounting for start-up costs

4.3.3 Data Inputs: Correspondence between written submission and electronic model

Transition probabilities

As already outlined, table 48 of the submission has only limited relevance to the electronic model. The transition probabilities that are applied in the original model are summarised in section 5.2.6 above. These have subsequently been heavily revised by the company as outlined in section 5.3.4 below.

Knee replacement quality of life values

Table 51 suggests a common quality of life value of 0.691 for all NFR subsequent to knee replacement health states. As already outlined above, this is incorrect. This value is only applied for those moving immediately from a 1st KR to NFR. Those moving to NFR from a 1st KR success, immediately from a subsequent KR, and from a subsequent KR success have a quality of life of 0.557 applied. This increases the cost effectiveness of a treatment which avoids knee replacements.

4.3.4 ERG commentary on model structure, assumptions and data inputs

Comparators

The AC of TA477 noted that those failing after a 1st microfracture repair would not receive a 2nd microfracture repair. The FAD of TA477 approved ACI with various restrictions, among them that "*the person has not had previous knee repair surgery*". This suggests that a comparator of only a 1st microfracture repair should be considered, and that ACI subsequent to microfracture should not be considered. This limits the relevant comparators of the company analyses to:

- MF
- SPHX->MF
- MACI->MF
- CC->MF
- SPHX->SPHX
- MACI->MACI
- CC->CC

It can be further argued that the FAD of TA477 may not permit 2nd repairs with ACI, it limiting ACI to patients who have "*not had previous knee repair surgery*". However this should refer only to previous procedures that damage the sub-chondral bone, and the ERG interpretation is that a 1st ACI repair can be followed by a 2nd ACI repair, but the FAD is ambiguous.

Model structure

Successes from a 1st repair cannot lose response and move into the NFR health state. To the age of 55 they can only exit to a 2nd repair. This is a fundamental difference from the model structure of Mistry et al. To put this more clearly into context, if the model is used to explore there only being 1st repairs all the successful repairs remain successes to the age of 55 after which a small proportion each year receive knee replacements. This will overstate the benefits of treatment successes compared to the model structure of Mistry et al.

Probabilities of 1st repair success failing and requiring a 2nd repair

The likelihood of failure and requiring a 2nd repair is based upon the 2 year trials' data and the NMA. These probabilities are applied through the model time horizon.

For the modelling of the MTA of ACI the AC requested that this applied publicly available time to event data. This appears to worsen the cost effectiveness estimates for ACI compared to microfracture.

Modelling microfracture success duration

The AC of TA477 was critical of microfracture failures being modelled by microfracture successes having a lower quality of life applied for years 5+ after the successful repair, and suggested that this might be better handled through the transition probabilities.

In the ERG reduced set of comparators, a microfracture repair is never followed by another repair (in line with NICE guidance, and a decision during the MTA that ruled out second MF). Up to the age of 55 microfracture repair patients cannot exit to another intervention. It is consequently reasonable to apply a reduced quality of life among these patients after the average duration of repair. The model applies this for years 5+ after the repair. The limitation of this is that the model structure does not permit the average duration of microfracture success to be explored, other than assuming that it is indefinite[7]. The company supplies a scenario analyses that applies the indefinite duration of microfracture success assumption, and the ERG will do likewise.

Application of the NMA relative risks of response

The relative risks of response are applied to the 2 year response rate of Spherox. This seems peculiar. The resulting 2 year probabilities or risks imply relative risks that are very different from those of the NMA. When these are based upon the Spherox probability of response of 81% they imply the probabilities of the 2nd to last row of the table below. The ERG will apply these values for its revised base case.

But there may be an argument that the resulting probabilities of response for ChondroCelect and MACI are infeasibly high. This is due to the Spherox trial probability of response for microfracture being much higher than those of the other trials. There may be an argument for applying the relative risks to the mean microfracture rate of the trials of 69.59%. This would imply the response probabilities of the last row of the table below. The ERG will apply these as a sensitivity analysis.

Table 24 Alternative ERG application of the NMA relative risks of response

	SPHX	CC	MACI	MF
Spherox 2yr probability of response Sphx(P_2)	[redacted]			
Relative risk (RR)	[redacted]	1.209	1.223	0.968
Company 1st repair 2yr probability of response $P_2 = 1-(1-Sphx(P_2))^{RR}$	[redacted]	86.57%	86.88%	79.98%
Relative risks implied by 2yr probabilities of response $P_2/Sphx(P_2)$	[redacted]	1.069	1.073	0.987
ERG 1st repair 2yr probability of response $P_2 = Sphx(P_2)*RR$	[redacted]	97.93%	99.06%	78.41%
ERG 1st repair 2yr probability of response P_2 with MF = 69.59%	[redacted]	86.88%	87.89%	69.59%

[7] This is a slight simplification for the company full set of comparators since there is the possibility of exiting to a 2nd repair. But this does not apply to the reduced set of comparators.

In response to a 2nd clarification the company states that: "*The original approach was an incorrect application of the NMA data*". The company supplies an alternative set of estimates and sources, but does not outline the arithmetic of these estimates. The last row of the table below contains the relative risks that appear to be implied by these estimates as calculated by the ERG.

Table 25 Alternative company estimates of response probabilities

	SPHX	CC	MACI	MF
1st repair 2yr probability of response P_2	[redacted]	91.59%	92.28%	78.44%
Source	NMA + OR from trial			NMA
Relative risks implied by 2yr probabilities of response P_2/Sphx(P_2)	1.000	1.152	1.161	0.987

The relative risks implied by the company revised estimates still appear to be different from the central estimates of figure 12 of the company submission and biased in favour of Spherox relative to MACI and ChondroCelect. The stated sources are also peculiar with the trials' odds ratios apparently being applied to the NMA. In the absence of further information (requested 10th October) about the revised company calculations the ERG will only apply these in a sensitivity analysis.

Application of the NMA relative risks of failure

The same considerations around the application of the NMA relative risks of failure as outlined above for the NMA relative risks of response apply. The company has applied these to rates rather than to probabilities. This is relatively minor due to the low probabilities of failure.

The ERG revises the model to apply the NMA relative risks of failure to the failure probability for Spherox as inputted to the NMA.

2 year probabilities of response for 2nd repairs

For 2nd repairs the probability of response is calculated as the square root of the 2 year probability of response. The intention here appears to have been that this should be compounded over 2 model cycles and so after 2 annual cycles result in the 2 year probability of response. But in the model every incident patient that gets a 2nd repair has this 2nd repair probability of response applied only once. This causes the model to overestimate the initial proportion of patients achieving successes and seems

likely to result in some bias in favour of ChondroCelect and MACI and some bias against microfracture.

Table 26 Probabilities of 2nd repair responses

	SPHX	CC	MACI	MF
Spherox 2yr probability of response $Sp(P_2)$		[redacted]		
Relative risk (RR)	1.000	1.209	1.223	0.968
1st repair 2yr probability of response $P_2 = 1-(1-Sp(P_2))^{RR}$	[redacted]	86.57%	86.88%	79.98%
2nd repair probability of response = $P_2^{½}$	[redacted]	93.04%	93.21%	89.43%

In the opinion of the ERG given the model structure the best mean of addressing this is to treat 2nd repairs as 1st repairs; i.e. to apply the 2 year probability of response to the incident patients during a single annual model cycle. While not correct, this is probably more correct than the original model implementation.

Derivation of the probabilities of 2nd successes becoming failures

The derivation of the annual probabilities of 2nd repair successes becoming failures is invalid. As previously outlined in section 4.2.6 above there are peculiar calculations based upon the initial 2 year probabilities of success. This results in typically fewer than half of successes being estimates to remain as such each year.

The company suggests revising this to apply the same probability of moving from a 2nd repair success to NFR as that of the 1st repair success to NFR. But, for example, this means that for SPHX->MF, the 2nd repair of MF has the probability of the 1st repair of Spherox applied to it. This seems peculiar and the ERG will revise this so that the probability a 2nd repair success becoming NFR is equal to the corresponding probability of a 1st repair of the same type, MF in this example.

But there is a more general problem with the company method. The 2 year probability of response or success, P_2, is treated as implying a probability of failure of $(1-P_2)$. For 1st repairs these probabilities are only applied during the first cycle. But for 2nd repairs the probability of failure, or the success going to NFR, is applied not just to the year of repair but every year. While this is correct at year 2, it is not obviously correct to extrapolate an ongoing failure rate using an annualised $(1-P_2)$. In the light of this the annualisation of the 2 year probability for 2nd repairs is retained by the ERG. There is no simple means of correcting this in the company model. But provided that the modelling does not consider MF->MF, an exploration that sets these probabilities to zero does not particularly affect the cost effectiveness estimates.

4.4 Exploratory and sensitivity analyses undertaken by the ERG

For the main analyses, as outlined at the start of section 5.3.4 above in the light of TA477 and its FAD the ERG reduces the list of comparator sequences to:

- MF with no 2nd repair
- SPHX->MF
- MACI->MF
- CC->MF
- SPHX->SPHX
- MACI->MACI
- CC->CC

It can be argued that TA477 does not formally bar Spherox as a 2nd repair after microfracture and that this should be considered. But the ERG thinks it unlikely to apply (the ICERS were higher than usually considered acceptable, though assuming cell cost of £16,000) and considering it within the set of comparator sequences adds relatively little to the analysis.

The company base case assumption that all microfracture repair successes lose all their quality of life gains at 5 years is central to the comparisons with microfracture. The company model structure does not permit this assumption to be relaxed such that the gains are lost gradually after 5 years. The TA477 AC expressed concerns around this assumption. It is sufficiently central for two full sets of analyses to be presented, one that assumes that all microfracture repair successes lose all quality of life gains at 5 years and one that does not[8].

The ERG has revised the company model to:

- Multiply the Spherox 2 year probability of response by the 2 year relative risks of response to derive the comparator 2 year probabilities of response.
- Apply the above 2 year probabilities of response to 2nd repairs, albeit within an annual cycle.
- Multiply the Spherox probability of failure and 2nd repair by the relative risks of failure and 2nd repair to derive the comparator probabilities of failure and 2nd repair.
- Remove the double halving of the 2 year probability of failure and repair for microfracture.
- Revise the probabilities of moving from a 2nd repair success to NFR to be based upon those of 1st repairs.
- Apply the quality of life values of Mistry et al for knee replacement.
- Apply the costs of the FAD of the MTA of ACI [TA477].

[8] This would also seem to require that the quality of life for success from an ACI 2nd repair after a microfracture 1st repair does not deteriorate after 5 years. But this is not considered in the ERG set of possible sequences.

All the clinical inputs derived from the trials and the company NMA have been heavily revised. The ERG has not been in this situation before. As already noted, the model is quite convoluted in its construction with a number of dead ends. It is desirable that the company spend some time checking the ERG model revisions before the 1st AC.

The ERG also undertakes the following sensitivity analyses:

- SA01: Pooling the MF response data across the three trials to yield an estimate of 70% and using the company NMA to provide estimates of 72% for Spherox, 88% for MACI and 87% for ChondroCelect.
- SA02: Applying the company revised estimates of the probability of response.
- SA03: No 2nd repairs.
- SA04: A 2nd MF repair after 1st MF repair being possible.

Given the concerns around the NMA, a head to head comparison of Spherox with microfracture would seem possible. For this the ERG applies the response probabilities of the COWISI trial.

4.4.1 ERG revised results: Microfracture successes lose all gains at 5 years

The ERG revised base case is as below.

Table 27 ERG base case CEAC: MF success lost at year 5

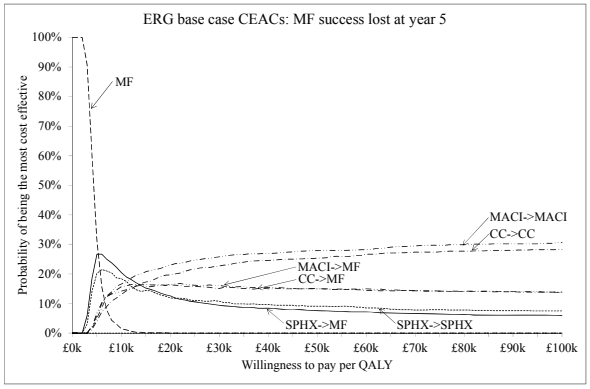
	Costs	QALYs	ICER
MF	£5,043	15.779	..
SPHX->MF	£15,980	17.989	£4,949
SPHX->SPHX	£16,987	18.035	Ext. Dom.
MACI->MF	£22,076	18.437	Ext. Dom.
CC->MF	£22,116	18.410	Dominated
MACI->MACI	£24,011	18.640	£12,336
CC->CC	£24,198	18.629	Dominated

The model suggests that ACI increases costs by roughly the extent of the cell costs. This is much as would be expected given that the harvesting and implantation costs are roughly the same as the costs of microfracture. The model estimates quite large QALY gains and SPHX->MF is estimated to be more costly than MF at £4,949 per QALY.

But MACI is more effective than Spherox, and the cost effectiveness of MACI->MACI relative to SPHX->MF is also good at £12,336 per QALY. At conventional willingness to pay thresholds MACI is estimated to be more cost effective than Spherox.

ChondroCelect is the same price as MACI but slightly less effective. This causes MACI to be estimated to dominate it. But this is better read as MACI and ChondroCelect being of much the same clinical effect and cost effectiveness.

Figure 6 ERG base case CEAC: MF success lost at year 5



The probabilistic modelling suggests that at low willingness to pay values microfracture has the highest probability of being cost effective. Spherox may be the most likely to be cost effective if the willingness to pay lies between £5k and £10k per QALY. At conventional willingness to pay thresholds MACI followed by MACI and ChondroCelect followed by ChondroCelect are more likely to be the most cost effective.

If the VerMACI and ChondroCelect ACIs, being of the same intervention cost and of similar effectiveness, were to be grouped the likelihood of these being the most cost effective would lie somewhat above that of the grouped Spherox likelihood.

None of the ERG scenario analyses change the cost ordering of the various strategies which eases their presentation. In what follows, SA03 does not permit a 2nd repair and as a consequence the label SHPH->SPHX is really just SPHX for this scenario, and likewise for MACI->MACI and CC->CC. Similarly, SA05 permits a 2nd MF repair after a 1st MF repair and so the label MF is really MF->MF for this scenario.

Table 28 ERG scenario analyses: MF success lost at year 5

	Base	SA01	SA02	SA03	SA04

MF	..	..	..	..	..
SPHX->MF	£4,949	£5,554	£5,030	n.a.	£4,791
SPHX->SPHX	Ext. Dom.	Ext. Dom.	Ext. Dom.	£4,360	Ext. Dom.
MACI->MF	Ext. Dom.	£15,310	Ext. Dom.	n.a.	Ext. Dom.
CC->MF	Dominated	Dominated	Dominated	n.a.	Dominated
MACI->MACI	£12,336	£15,177	£18,284	£12,180	£12,336
CC->CC	Dominated	Dominated	Dominated	Dominated	Dominated

SA01 reduces the microfracture response rate to the average across the three main trials, with the response rates for the ACIs being based upon this coupled with the relative risks of the company NMA. This worsens the cost effectiveness of ACI in general compared to microfracture. This in turn causes MACI-MF to no longer be dominated.

SA02 applies the company revised response estimates. This has little effect upon Spherox and microfracture but it worsens the effectiveness of MACI and ChondroCelect. As a consequence, the cost effectiveness of MACI->MACI relative to SPHX->MF worsens to £18,248 per QALY.

SA03 only compares 1st repairs with no 2nd repairs being possible. This slightly improves the cost effectiveness of Spherox relative to microfracture due to SPHX being estimated to result in slightly greater total QALYs than SPHX->SPHX. This would appear to raise some concerns around the modelling of 2nd repairs, but it may rather be a reflection of the modelling of 1st repairs not permitting patients to move from a successful repair into the NFR health state. If there are no 2nd repairs patients remain trapped in the 1st repair success health state.

SA04 permits a 2nd microfracture repair after a 1st microfracture repair. This slightly worsens the cost effectiveness of MF->MF and as a consequence the cost effectiveness of SPHX->MF relative to MF->MF improves slightly.

4.4.2 ERG revised results: Microfracture successes do not lose all gains at 5 years

The ERG revised base case is as below.

Table 29 ERG base case CEAC: MF success not lost at year 5

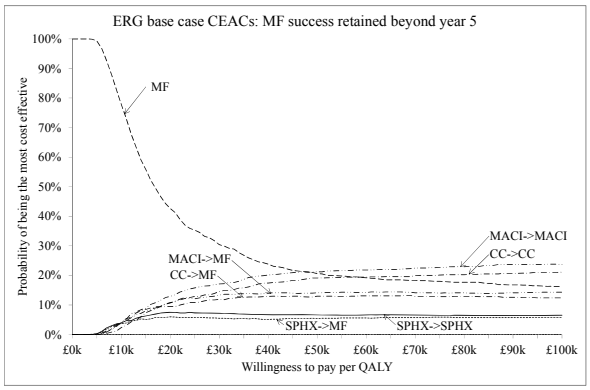
	Costs	QALYs	ICER
MF	£5,043	18.119	..
SPHX->MF	£15,980	18.036	Dominated
SPHX->SPHX	£16,987	18.035	Dominated
MACI->MF	£22,076	18.494	Ext. Dom.

CC->MF	£22,116	18.472	Dominated
MACI->MACI	£24,011	18.640	£36,425
CC->CC	£24,198	18.629	Dominated

The costs are as per the previous analyses. But the total QALYs for microfracture increase quite markedly to be roughly the same as those for Spherox. This is much as would be expected given the small difference in response rates between microfracture and Spherox.

The model formally estimates a higher total QALY for microfracture than for Spherox followed by microfracture, despite microfracture having a very slightly lower response rate than Spherox. In the opinion of the ERG this is due to the model in the absence of 2nd repairs causing 1st repair successes to remain successes indefinitely and none to lose response and move into the NFR health state. This view is given some support by SA03 below which only models 1st repairs for all comparators and causes the total QALYs for Spherox to rise very slightly above those of microfracture.

Figure 7 ERG base case CEAC: MF success not lost at year 5



The probabilistic modelling suggests that at a willingness to pay of £30k per QALY microfracture remains likely to be the most cost effective by a reasonable margin. But this is to compare microfracture with the individual ACI sequences. The probability of microfracture being the most cost effective falls below 50% at willingness to pay values above around £15,000 per QALY. But even at £30k per QALY its probability of being the most cost effective is still about 30%.

If the conventional ACIs, being of the same intervention cost and of similar effectiveness, were to be grouped the absolute separation between these and the grouped Spherox would increase.

Table 30 ERG scenario analyses: MF success not lost at year 5

	Base	SA01	SA02	SA03	SA04
MF	..	..	..	..	..

SPHX->MF	Dominated	Dominated	Dominated	n.a.	Ext. Dom.
SPHX->SPHX	Dominated	Dominated	Dominated	Ext. Dom.	Dominated
MACI->MF	Ext. Dom.	Ext. Dom.	Ext. Dom.	n.a.	Ext. Dom.
CC->MF	Dominated	Dominated	Dominated	n.a.	Dominated
MACI->MACI	£36,425	£51,698	£71,489	£29,349	£20,601
CC->CC	Dominated	Dominated	Dominated	Dominated	Dominated

The pattern of dominance is retained throughout the scenario analyses. Microfracture is estimated to result in slightly higher total QALYs than SPHX->MF and SPHX->SPHX. But the differences are small and as for the base case this is probably more accurately seen as Spherox resulting in similar total QALYs as microfracture but at somewhat greater cost.

SA01 reduces the response probability for MF. Applying the relative risks from the NMA, reduces the response for MACI. This in turn worsens the cost-effectiveness of MACI>MACI relative to MF. SA02 applies the company revised response probabilities for MACI which are worse than those of the company's base case. This again worsens the cost-effectiveness of MACI.MACI relative to MF.

SA03 causes the total gains for Spherox to rise slightly to 18.189 QALYs and so be greater than the 18.119 QALYs of microfracture. But its cost effectiveness compared to microfracture is poor at £150k per QALY.

More surprising for SA03 is the extent of the improvement in the cost effectiveness of MACI relative to MF if there are no 2nd repairs. The net QALY gains of the base case are much reduced if microfracture success is not assumed to be lost at 5 years. The small increase in total QALYs changing from MACI->MACI to MACI has a larger proportionate effect. SA04 also provides similar cause for concern in terms of the modelling of 1st repairs compared to 2nd repairs as outlined in section 5.4.1 above.

The results of SA04 that models a 2nd MF repair after a 1st MF repair are also surprising. The cost effectiveness estimate drops quite markedly. But this appears to be due to the handling of the probabilities of 2nd repair successes moving into NFR. If these probabilities are set to zero the cost effectiveness of MACI->MACI relative to MF->MF still falls, but only to £29,062 per QALY.

4.4.3 ERG revised results: Spherox head to head with microfracture

In the light of the problems with the modelling of 1st repairs compared to 2nd repairs this section considers both MF against SPHX->SPHX and MF against SPHX.

Table 31 MF against SPHX->SPHX

	MF success lost yr5		MF success not lost yr5	
	Costs	QALYs	Costs	QALYs
MF	£5,043	15.779	£5,043	18.119
SPHX->SPHX	£16,987	18.035	£16,987	18.035
net	£11,944	2.256	£11,944	-0.084
ICER	£5,294		Dominated	

Table 32 MF against SPHX

	MF success lost yr5		MF success not lost yr5	
	Costs	QALYs	Costs	QALYs
MF	£5,043	15.779	£5,043	18.119
SPHX	£15,549	18.189	£15,549	18.189
net	£10,506	2.410	£10,506	0.070
ICER	£4,360		£150,506	

The broad conclusion from the above is that if microfracture success persists, there is little clinical difference between microfracture and Spherox. If so, the cost effectiveness of Spherox relative to microfracture is estimated to be poor. But if microfracture success is lost at 5 years the cost effectiveness of Spherox relative to microfracture is estimated to be good.

The results of this section should be viewed with caution and alongside the validation data presented in section 5.2.11 above.

Rehabilitation costs

There is a comment on page 92 of the Co-Don submission that rehabilitation needs are reduced compared to other forms of ACI, as a result of the less invasive surgical procedure.

We doubt that. The rehabilitation after the surgery (in effect, wound healing) is unimportant compared to the rehabilitation associated with maturation of the cartilage in the defect. And MACI can also be done by mini-arthrotomy.

We note comments in various places in the CoDon submission that patients were required to adhere to a strict rehabilitation programme. (And that they should not receive ACI unless they agreed, which is sensible. One of our clinical advisors in the MTA had problems with keen sportsmen returning to sport too soon and damaging the repair.) We also note that in Table 53, the same number of rehabilitation visits is assumed for Spherox and MACI. And on pages 117 and Table 2, rehabilitation is envisaged to take up to a year, as with MACI.

Most rehabilitation is actually patients doing exercises at home at no cost to NHS.

The bottom line is that we do not think there is any significant difference in rehabilitation duration or costs between Spherox and MACI.

4.5 Conclusions on cost effectiveness

The model structure differs from the model structure of the ACI MTA [TA477] in one fundamental aspect. It is not possible for 1st repairs successes to subsequently lose response and patients to move into the no further repair health state. This seems likely to bias the model in favour of the more effective treatment. When coupled with the assumption that all microfracture successes fail at year 5[9] it is also likely to bias the analysis in favour of Spherox compared to microfracture.

The ERG has attempted to revise the company model to have inputs similar to those of the 1st AG report of the ACI MTA. This is imperfect but appears to suggest that the company model estimates roughly double the patient gains compared to the model of the 1st AG report of the ACI MTA. The company model structure may be too optimistic for the comparison with microfracture.

Over the course of the ACI MTA the model inputs evolved. The AC requested that publicly available time to event data be used to estimate the probability of loss of response. The cost effectiveness estimates also appear to worsen over the course of the ACI MTA. Not reflecting the publicly available time to event data may mean that the company model is again too optimistic for the comparison with microfracture.

For 2nd repairs the probability of response is only applied once and as a consequence the company method to derive the estimates appear to be too high. This biases the analysis in favour of MACI and ChondroCelect. The ERG changes this in its revised base case.

For 2nd repairs the possibility of a success losing response and moving into the NFR health state is allowed for in each cycle. The original company estimates for this were incorrect. The revised company estimates are more reasonable. But they are still based upon data that does not particularly relate to this aspect of the model and may be too high. If the model is revised to permit 1st repair successes to lose response with the probability of this being derived from publicly available time to event data, this would probably be the best source for 2nd repairs as well.

The clinical effectiveness of MACI and ChondroCelect is similar. They are assumed to have the same costs. For the probabilistic modelling it may be clearer to consider these as a single treatment.

[9] While this sounds like microfracture successes are failing and so moving into the NFR health state, the model implementation is that they remain successes but have a lower quality of life value applied to them from year 5.

The application of the relative risks of the company NMA is wrong. The resulting company estimates imply relative risks that differ from those of the NMA and that are biased in favour of Spherox. The company has supplied a revised set of response estimates but does not explain their calculation. They still appear to imply relative risks that differ from those of the NMA and that are biased in favour of Spherox.

The ERG revised base case applies clinical effect estimates for both 1st repair and 2nd repair that differ quite markedly from those of the original model and that differ from the company revised response estimates. The ERG has also revised the unit costs to reflect those preferred during the ACI MTA.

In the COWISI trial, [redacted]. Virtually all the modelled gains are a consequence of the assumption that all microfracture successes fail at 5 years. If this is applies the company model estimates that the cost effectiveness of Spherox compared to microfracture is very good. But the company model estimates that MACI yields additional patient gains albeit at a higher cost, and the cost effectiveness of MACI relative to Spherox is also good. If microfracture repairs are as durable as ACI repairs the company model estimates the cost effectiveness of Spherox to be poor.

5 Discussion

5.1 Principal findings

The principal findings in this report are;

- Spherox is clinically effective in the treatment of chondral defects
- However, the phase III COWISI trial has not yet, at 24 months, [redacted]
- The Phase II dosage study shows that the benefit of Spherox implantation varies little by dose, and that the benefit is sustained for up to 4 years
- Around [redacted] of the defects treated in the Phase 2 study were patellar.
- We think the network meta-analysis was inappropriate due to heterogeneity of the included trials
- Taking the above into account, we are doubtful that there is sufficient evidence of benefit to support the economics modelling
- The Appraisal Committee may take a more sympathetic view, so we have critiqued the Co-Don modelling
- The company model structure differs from that of the ACI MTA in that it does not permit 1st repair successes to lose response and move into the no further repair health state. This seems likely to bias the model in favour of the more effective treatments. When coupled with the assumption that all microfracture fails at 5 years it seems likely to bias the analysis in favour of Spherox compared to microfracture.
- ERG validation work suggests that the company model may overestimate the patient gains from ACI relative to microfracture compared to the model of the 1st AG report to the ACI MTA. The modelling of the ACI MTA also evolved to incorporate time to event data. The cost effectiveness estimates appear to have worsened over the course of the ACI MTA. The company model may consequently be too optimistic.
- The company application of relative risks is incorrect and biased in favour of Spherox. The company has supplied revised estimates for the probabilities of response. These still appear to be biased in favour of Spherox.
- The modelled patient gains from Spherox over microfracture are almost entirely due to the assumption that all microfracture successes fail at year 5. These gains cause the company model to estimate Spherox to be cost effective relative to microfracture. But MACI results in greater gains albeit at a higher cost, and the company model estimates that its cost effectiveness relative to Spherox is good.

- If microfracture repairs are as durable as ACI repairs the cost effectiveness of Spherox compared to microfracture is poor.

5.2 Differences in results with microfracture.

The COWISI trial found [redacted] in outcomes between ACI and MF at 24 month. For example, the median changes in KOOS scores from baseline were [redacted] points. This may not be surprising since MF is usually effective in the short term. The 5-year ACTIVE trial results, presented at the 11th Oswestry Cartilage Symposium on 5th October 2017 (Samir Mehta, personal communication), reported no significant differences between ACI and control groups (mainly MF) at 5 years.

However, the trials of ChondroCelect and VeriMACI examined in the recent MTA of ACI, did show some differences at 2 years. In the SUMMIT trial, the 24 month results included;

- Responders 87.5% with MACI, 68.1% with MF
- KOOS subscales all statistically significantly better with ACI
- No failure with MACI, two with MF
- Cincinnati scores 1.05 points better with MACI (p =0.002)
- IKDC 5.9 point better with MACI (p = 0.069)
- But no difference in EQ5D

In the TIG/ACT trial at 24 months, KOOS scores had improved by about 20 points after ACI and by about 13 points with MF, with no overlap of 95% Cis. There were two failures with ACI and 8 with MF.

The COWISI, TIG/ACT and SUMMIT trials differed in the characteristics of participants as reported earlier. For example, a possible explanation for the poorer results of MF in SUMMIT compared to COWISI is the defect sizes, with [redacted] defects in COWISI (mean [redacted]) than in SUMMIT (mean 4.9cm^2, and all over 3cm^2).

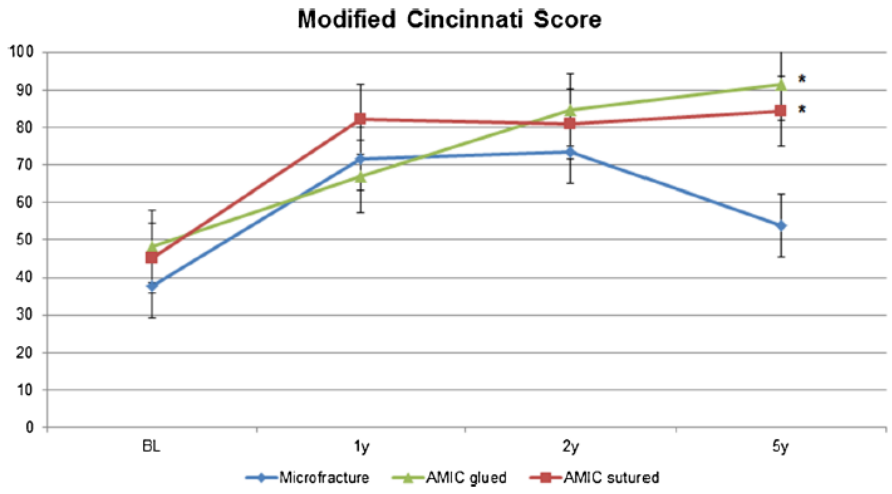
The ERG view is that the benefits of ACI compared to MF are seen mainly in later years. Longer-term data from the ACTIVE trial are not yet published. Evidence from observational studies was reported in the assessment report for the MTA, but in brief;

- Solheim and colleagues [59] reported 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

- Many people with chondral defects are sportsmen or women and return to sport is a useful outcome. Two good quality systematic reviews by Campbell and colleagues[60] and Krych and colleagues[61] reported that proportions returning to sport were higher with ACI than MF – 84% versus 75% (Campbell) and 82% versus 58% (Krych) . 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.
- A systematic review by DiBartola and colleagues[62] reported poorer histological outcomes after microfracture compared to ACI. However, there were only six studies of MF compared to 30 of ACI.
- A very large follow-up study by Layton et al[63] of over 3000 patients in routine care who had MF, reported failure rates (defined as requiring further surgery) of 9% within one year, 18% by 3 years, and 32% by 5 years. Others did not have further surgery, but required powerful analgesics.
- A recent study by Volz and colleagues[64] reported that most of the benefits of MF were lost by 5 years.

Figure 8 Modified Cincinatti Score (from Volz et al 2017)

Fig. 3 Modified Cincinnati score. Number of patients available at five years follow-up (n): Microfracture (9), AMIC glued (14, p = 0.002), and AMIC sutured (16, p = 0.01); * significance versus Microfracture at five years



Conversely the 15-year results from the Knutsen trial[45] reported that long-term results with MF were as good as with ACI, though only 40 patients were randomised to each arm.

The assessment group in the MTA took a "middle view" on duration of benefit of MF, being more optimistic than the SUMMIT and TIG/ACT trials, less optimistic than the Knutsen 2016 study, and close to the Volz et al 2017 study.

5.3 Is Spherox more effective in patellar lesions than other forms of ACI?

ACI has been regarded as less successful for patellar lesions than condylar ones though results have been improving.[65]

The patello-femoral joint has features that would potentially make good results more difficult to achieve, including a less congruous joint surface which is made even more difficult in the (common) setting of a mis-shapen trochlea or patella (trochlear dysplasia or patellar dysplasia). The joint also undergoes high contact loads and shearing forces, explaining why the cartilage in a healthy knee is thickest under the patella. It is possible that ACI with caps (ACI-C) or matrices (MACI) more be more likely to be sheared off than spheroids, and this may be a plausible explanation for a difference in results in this region.

We cannot compare results in patellar and condylar lesions from the available trials. The SUMMIT trial recruited mainly medial femoral condylar defects, with small numbers of lateral femoral condylar and trochlear defects. In TIG/ACT all recruits has femoral condylar lesions. In ACTIVE, only 12% had patellar or trochlear problems. In the COWISI trial primary defects were all condylar, but there is no comparison of results by condyle.

The data on [redacted] comes from the phase II dosages trial. The CSR mentions, but does not include, some tables of results by site. The text includes KOOS results to visit 8, which are as good for patellar as for condylar defects. [redacted] of recruits in the Spherox Phase II dosage trial had patellar lesions. The Co-Don submission does not provide separate data for the two condyles.
Nawaz et al[66] reported that best results came from lateral femoral condylar defects, with little difference in outcomes after treatment of MFC and patellar defects.
In conclusion, Spherox may be better in patellar defects than older forms of ACI, but we do not currently have clinical effectiveness evidence that would support any cost-effectiveness comparison.

5.4 Extrapolation from older forms of ACI

In our assessment report for the ACI MTA, we reviewed long-term results of previous generations of ACI. We assumed that the long-term results of third generation ACI would be at least as good as first generation ACI-P. All the first three generation were based on implanting chondrocytes which then produced cartilage in vivo. Can we extrapolate from cell implants to spheroid implants? The question here is whether the spheroid cartilage integrates as well with the cartilage surrounding the defect, as the cartilage produced after MACI. There is evidence from basic science studies that provides reassurance that this is the case, so it appears that we do not need to worry about possible weaknesses around the "join".

5.5 Could a pragmatic case be made for Spherox?

To recap.

1. We know that Spherox works, in the sense that it improves patient symptoms as reflected in scores such as KOOS. This has been shown in the two trials and in the before and after case series.
2. The benefit is sustained for at least 4 years as in the Phase 2 trial of different doses, in patients with large defects.
3. The evidence from trials and case series suggests that there are no serious safety concerns.
4. The main problem is comparative effectiveness. [redacted]. This is perhaps not surprising since MF works in the short-term, and the smaller the defect, the more competitive MF is with ACI. The results from the ACTIVE trial, first released on 5th October 2017 at the UK meeting of the International Cartilage Repair Society (ICRS) and *Arthritis Research UK Tissue Engineering Centre* (ARUK TEC) in the RJAH Orthopaedic Hospital in Oswestry, show no advantage over MF at 5 years.
5. The assessment group report for the ACI MTA concluded that in the longer-term, the benefits of MF were not sustained, but that the benefits of ACI were, albeit varying amongst patients (hence the restricted approval). The Appraisal Committee had concerns about the quality of the evidence base for comparing long-term outcomes of ACI and MF, but did recommend that ACI be used.

Given the above, it could be argued that the lack of evidence of cost-effectiveness of Spherox is due to lack of long-term results, and that with longer follow-up, it would achieve acceptable ICERs.

5.6 OsCells

The Co-Don submission does not mention OsCells or the ACTIVE trial, which is fair enough given that the trial has not yet been published, and that data used in the recent MTA was academic in

confidence and not available to Co-Don. One issue is whether OsCells should have been included as a comparator. The ERG view is that OsCells are not a comparator because they are not available outwith the RJAH Orthopaedic Hospital. (And in the ACTIVE trial, most cells were provided by Genzyme.) The data on OsCells could be used to illustrate the potential for production of cells in other NHS facilities but those would take time to set up because of the regulatory burden.

5.7 Age limits

The upper age limit in COWISI was 50. In our last report on ACI for NICE, we noted that Filardo and colleagues have suggested that the consensus against ACI in older patients should be challenged.[67] Filardo and colleagues analysed results in their series of 157 patients treated with MACI, after excluding any with OA (defined as 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. They note that some previous 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.

This appraisal specifies use of ACI in adults, 18 years and over. As noted in the recent MTA, there is some evidence of benefit from older forms of ACI in teenagers, and we have noted that the studies of Spherox in people aged under 18.

5.8 Research needs

The COWISI trial. The most important research need is for longer-term follow-up of the COWISI trial, but this is planned. We note that the ICRS has set up a registry for long-term follow-up of ACI and other knee procedures, and if Spherox is approved (now or later), it could be under condition that patients are registered with ICRS so that long-term data will accrue.
The aims of the ICRS registry[68] are:

Our mission is to create the best source of unbiased outcomes data for treatments of painful articular cartilage lesions in the world, which is paramount for improvement of existing and discovery of new cartilage repair strategies, ultimately beneficial for millions of patients around the world.

The ICRS Registry is a mechanism of allowing you and your doctor to track your individual progress following diagnosis and/or treatment of your knee problem. It is suitable for anyone with cartilage damage, whether or not the cartilage damage itself is treated. The response of patients to cartilage damage and treatments can be variable, treatments can also be forefront of medical advances, many are expensive. It is vital to you and your doctor that your progress is monitored. With your permission, the ICRS Registry makes your data anonymous so you cannot be personally identified, and pool together large numbers of patients results so that doctors around the world have the most accurate picture of which techniques are working best in which patients.

This helps patients of the future with similar injuries or cartilage problems, and rapidly identifies treatments that are showing great benefit, those that may not be performing as well as hoped, and also what happens naturally if nothing is done.

The cost-effectiveness of ACI is driven by the duration of repair success for MF, Spherox, VerMACI and ChondroCelect. The ACTIVE trial will provide 10-year data on outcomes after MF and ACI in a few years. Any economic modelling of Spherox based on the CTIVE results would probably have to assume the same duration of repair success for Spherox as for the ACI in ACTIVE.

Defects smaller than 2cm^2.

The British Knee Surgeons consensus considered that interventions such as MF and mosaicplasty should be considered in defects < 2cm^2, stating

"In the absence of comparative trials in small lesions showing superiority of cell therapy, the cost of cell therapy would need special circumstances to justify use."

The SUMMIT trial included only people with defects of 3 cm^2 or greater. The TIG/ACT trial included defects in the range 1-5 cm^2 with mean area 2.6 cm^2 in the ACI arm, but did not give a breakdown of results by defect size. The COWISI trial includes defects between1-2cm^2 but numbers are small.

There is therefore a case for a trial of ACI versus microfracture in small lesions, with follow-up for at least 5 years, and with a cost-effectiveness analysis.

Can results of ACI be improved?

Another issue is whether results of cartilage repair can be improved. In the third assessment report for the recent MTA of ACI, we noted that return to sporting activity was a useful indicator of success. Campbell and colleagues[60] 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[61, 69] 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). Krych et al concluded that 82% returned to sport at some level after ACI compared to 58% after MF.

However return to sport may not be at the level reached before injury. In a good quality review, Schmitt and colleagues[70] reviewed a number of indicators of performance, including muscle (mainly quadriceps) strength and performance achieved, after cartilage repair procedures, both MF and ACI. They found that significant quadriceps strength deficits and functional shortfalls were common 5-7 years after repair procedures. This does not necessarily mean that the repairs were the problem – it could be that the injury and resulting inactivity were the reasons. However they conclude that research is needed into why previous function was not restored, and into different rehabilitation regimens. They do note that one possible reason is impatience, with some sports-people starting weight-bearing and then activity too early.

Can success be predicted before implantation?

The chondrocyte cells from each patient are cultured in the laboratory and encouraged to grow spheroids of cartilage, which are then implanted. Some patients have better results than others. If we could predict failure before implantation, then the implantation cost could be avoided and the spheroids discarded.

Co-Don have done work on this, looking at biomarkers for chondrogenesis in the spheroids and the culture serum. Some of this has been promising but inconclusive. Glycosaminoglycans (GAGs) are one component of the extracellular matrix in hyaline cartilage, and contribute to the shock-absorbing function of cartilage. Bartz et al[71] measured the GAG content of spheroids and of the surrounding culture medium, and found variations, in cultures from different donors, in the proportions of GAG retained in the spheroids or released into the culture serum. A low bound to retained ratio was associated with poorer regeneration after implantation, but showed a trend rather than being sufficiently predictive of failure.

However another component of hyaline cartilage, aggrecan (which is the main proteoglycan in extracellular matrix of articular cartilage – Fox et al[72]) did show a stronger correlation with successful regeneration. A high level of aggrecan in spheroids before implantation was associated with a better repair.

Measurement of biomarkers may have potential for development as a method for triage of spheroids before implantation, which might improve cost-effectiveness.

Source of chondrocytes

In the assessment report for the recent MTA of ACI, we noted the work of Mizuno and colleagues [73], using chondrocytes from the ear, so far only in dogs. We also note the work of Mumme and colleagues[74] in humans, using nasal chondrocytes to produce cartilage grafts for ACI. At the 11th Oswestry Cartilage Symposium in October 2017, Ivkovic from Zagreb (personal communication) presented further work on "nose to knee" ACI.

This is another example of the problems in the evaluation of evolving technologies such as ACI. Lilford et al[75] outlined the problems;

"When should researchers start a randomised controlled trial in a clinical area where there is rapid technological change? Start too early and the resultant comparisons may seem likely to turn out to be irrelevant, but start too late and the chance of collecting much good quality data will have been lost, perhaps forever if clinical opinion has "gelled" despite the absence of randomised controlled trial data. The problem is compounded by the consid-erable time it takes to design, commission, and establish a full scale clinical trial."

They concluded that there was a need for "tracker trials" that allowed for evolution of the technology under study, without prefixed sample size or duration, and with interim analyses. However getting such trials funded may be difficult.

New forms of microfracture

Research into the reasons for differing results of MF from past studies may not be a high priority, since new methods of microfracture are being trialed, such as AMIC (autologous matrix-induced chondrogenesis). Volz et al[64] compared microfracture alone (13), or MF with a collagen cap (ChondroGide) either glued (17) or sutured (17) in place, in 39 patients. Mean defect size was 3.6cm^2, range 2.1 to 6.6cm^2, quite large for MF. In symptoms and function, all groups improved by 2 years, but improvement was sustained at 5 years in the capped group, but not in the standard MF group whose Cincinnati scores had declined by 5 years with over half the benefit at 2 years lost. Defect filling assessed by MRI at 5 years showed better filling in the capped group.

A trial by Shive and colleagues[76] 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).
Given the high cost of ACI, further research into enhanced MF may be worthwhile.

5.9 Conclusions

There seems to be no doubt that Spherox implantation is beneficial in chondral defects, but its comparative efficacy is as yet uncertain.

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7 Appendices

Appendix 1.

Quality assessment of the COWISI trial

The ERG's quality assessment of the COWISI trial used the Cochrane ROB tool [77] (Table 33). The quality assessment focused on the primary outcome, namely the change of overall KOOS from baseline to final 24 months after the end of the treatment.

Table 33 Quality assessment of the COWISI trial

Domain	Description	Assessment of risk of bias
Random sequence generation	"A randomisation list was prepared and retained by Statconsult GmbH". Little detail given.	Probably low
Allocation concealment	Central telephone randomisation was used to assign patients to one of the two groups	Low
Blinding of participants and personnel	Blinding was not practical for the primary outcome because MF requires only one procedure and Spherox has two.	High
Blinding of outcome assessment	The primary outcome was the change of overall KOOS which was rated by patients that were aware of the treatment allocation. Those allocated to MF might have been disappointed?	High
Selective reporting	The primary outcome was pre-specified and reported consistently. All outcomes were reported in 2.6.1	Low
Incomplete outcome data	No imbalance in study discontinuations between the two arms.	Low
Other bias	The study was funded by Co-Don	Uncertain

Appendix 2. Quality assessment of case series

Before-after (pre-post) studies with no control group. Fickert 2012.

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	X		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	X		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	X		Note 1
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		X	Note 2
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	X		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	X		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		X	Note 3
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?		X	Note 4
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	X		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	X		Note 5
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating: Fair
Additional Comments: Notes

1. Not entirely clear, but the patients recruited were a wider range than seen in trials, for example BMI and age range and on the second page, foot of RH column, they do say "patients from daily practice " etc.
2. The sample size was large enough for some results to be statistically significant, but with only 37 patients, extrapolation to larger use may be unsafe.
3. There is mention of "independent readers" but since they knew that all patients had had Spherox, we think blinding was impossible. The "independent" appears to refer ti duplicate assessment. And the patients could not be blinded. So outcome blinding unclear, but unlikely. If unblinded, then MRI findings likely to be at high risk of bias
4. Loss to FU 19% but no account given of why lost.
5. Multiple times after intervention but not before. But methods comparable with most ACI studies.

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

Before-after (pre-post) studies with no control group. Maotti 2012

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?		X	
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		X	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			N/A
5. Was the sample size sufficiently large to provide confidence in the findings?		X	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?			CD
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	X		Note 1
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	CD note 2
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			NR
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	X		

11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			CD
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating: Poor
Additional Comments: Abstract only, therefore unable to determine many domains. Notes. 1. Yes overall. Yes for pre-specified, clearly defined and reliable, no for consistent assessment 2. Both a no and CD, because some outcomes assessed by patients who knew what they had had, and others assessed by radiologists or histology with no details given.

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

Before-after (pre-post) studies with no control group. Siebold 2015

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	X		
2. Were eligibility/selection criteria for the study population pre-specified and clearly described?	X		
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?			CD Note 1
4. Were all eligible participants that met the prespecified entry criteria enrolled?	X		
5. Was the sample size sufficiently large to provide confidence in the findings?			CD
6. Was the intervention clearly described and delivered consistently across the study population?	X		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	X		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		X	

9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?		X	Note 2
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		X	Note 3.
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		X	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating: Fair
Additional Comments: Reasonable design and conduct Notes. 1. The series was of all patients who had arthroscopic assessment after ACI. No information is given as to whether this was done in all patients receiving spheroids. 2. Only 76% had clinical follow-up 3. No pre-op data provided.

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

Autologous chondrocyte implantation with Spherox for treating articular cartilage defects in the knee. (NICE ID 851)

Warwick Evidence ERG report October 19th 2017 – **Erratum to the original report (November 20th 2017).**

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Contribution of authors;
Norman Waugh and Xavier Armoiry wrote the clinical effectiveness section, assisted by Jeremy Rodrigues. Norman Waugh co-ordinated the project and wrote Chapters 1 and 5. Ewen Cummins wrote the cost-effectiveness section, assisted by Rhona Johnston and Hema Mistry. Pamela Royle conducted literature searches. Andrew Metcalfe provided expert advice and commented on drafts. Norman Waugh and Pamela Royle edited the final document.
Text highlighted in yellow is academic in confidence.

There are no sensitivity analyses around the revised company estimates. The original modelling was most sensitive to the assumption that all microfracture repair successes fail at year 5.

1.5 Summary of the ERG critique of the cost effectiveness evidence submitted by Co-Don

The company model differs from that of the model of the ACI MTA in one crucial respect. 1st repair successes cannot lose response and move into the no further repair health state. This is likely to bias the analysis in favour of the ACIs. It may also further bias the analysis in favour of MACI and ChondroCelect if their loss of response is similar to that of Spherox, because their initial success proportion is a bit higher.

The response estimates for 2nd repairs are only applied once within the modelling and as a consequence the company method used to derive these is incorrect.

The company accepts that the probabilities of 2nd repair successes losing success and moving to no further repair are incorrect. It suggests revising these to be based upon the annualised 1st repair non-response probabilities at 2 years. These estimates are applied every year of the model, do not really relate to a loss of response, and are probably too high.

The company clinical effectiveness estimates are incorrect and biased in favour of Spherox.

The company quality of life estimates are aligned with those of the ACI MTA.

The company does not apply the preferred set of unit costs of the ACI MTA FAD.

1.6 ERG commentary on the robustness of evidence submitted by Co-Don

The ERG has attempted to revise the company model to have inputs similar to those of the 1st AG report of the ACI MTA. This is imperfect but appears to suggest that the company model estimates roughly double the patient gains compared to the model of the 1st AG report of the ACI MTA. The cost effectiveness estimates of the ACI MTA also tended to worsen as the assessment progressed and publicly available time to event data for loss of response was incorporated. The company model structure may be too optimistic for the comparison with microfracture.

The company accepts that all the clinical effectiveness estimates for the model of its original submission were wrong and biased in favour of Spherox. It has provided a revised set of estimates for a subset of these. These still appear to be incorrect and biased in favour of Spherox.

The second generation of ACI used a collagen cap (ACI-C) instead of the periosteal one, but still used cells in a liquid suspension

In the third generation of ACI, the chondrocyte cells are loaded or embedded, or "seeded", on to a porcine collagen membrane ACT-C or matrix (MACI – matrix induced chondrocyte implantation), with a patch cut to fit. These patches can be implanted by a less invasive form of surgery, by mini-arthrotomy, requiring less surgical time than ACI-C.[1] (Arthrotomy = opening of a joint). This has become the main method used.

The membrane used in MACI is composed of type I/III collagen, with a rough side wherein the chondrocytes are seeded and a smooth side which faces into the joint cavity.[17] The membrane is tough enough to be cut to shape or stitched in place, though it is more often glued in place.[17] The membrane is bio-degradable. The term "scaffold" is often used instead of membrane. However the membrane needs careful handling to minimize chondrocyte death during implantation. [18]

Box 2. The evolution of ACI

First generation	ACI-P. Liquid suspension of cultured chondrocyte cells placed in the defect covered with a cap made from periosteum.
Second generation	ACI-C. Liquid suspension of cells placed in the defect and covered with a collagen cap.
Third generation	The cultured cells are seeded on to a membrane or "scaffold" as in MACI (matrix associated chondrocyte implantation).
Characterized chondrocytes	Not all chondrocytes are equally good at producing cartilage. Some are more "chondrogenic" (cartilage-producing) than others. The most useful can be selected and are known as "characterized".
Fourth generation	Newer developments include the implantation not of cells that will form cartilage, but of tissue-engineered cartilage grown from autologous chondrocytes in the laboratory. Some of the chondrocytes used may come from cartilage from the nose or ear.

Spherox (formerly known as Chondrosphere and ACT3D) is a form of fourth generation ACI in which the cells are not only multiplied in the laboratory, but are persuaded to generate cartilage. Chondrocytes are harvested from healthy articular cartilage, cultivated for 6-8 weeks in the laboratory, and condensed into spheroids (chondrospheres) of cells plus cartilage. The 3-dimensional spheroids are then implanted into the defect. The Co-Don submission says that the spheroids adhere to

- The number of non-responders in both the trials was >30%, and since Spherox required two operations compared to one for MF, benefit for patients was not demonstrated.
- The dissenters was also concerned about production processes and whether problems therein were related to non-responder rates.

Note that at the time Spherox was being considered, only 12 month data from the COWISI trial were available, and the dissenters stated that the 24 month data were required before the benefit/risk assessment could be completed. So some may not now dissent.

The price of the spheroids is given as £10,000, and this is not flagged as confidential. It includes transportation costs. Harvesting and implantation costs are added and Co-Don have used the costs from the recent MTA, adjusted for inflation. This is despite an assertion (page 19) that Spherox requires less invasive surgery for implantation, arthroscopically or by mini-arthrotomy, which may result in less theatre time.

However MACI can also be done by mini-arthrotomy. (And arthroscopically, but cell viability and speed are better when ACI is done by mini-arthrotomy than arthroscopically.[36]
Several of the case series from Germany report that Spherox can be implanted arthroscopically, so we can accept that a slightly shorter operation is required, perhaps saving 10 minutes of theatre time. This will have little effect on overall costs.

1.7 Clinical effectiveness - trials

The Co-Don submission presents the results from two trials, one Phase II and the other phase III, but mentions some earlier case series in an appendix. They carried out systematic searches for studies, using what we consider to be reliable search strategies. No systematic reviews of Spherox were found.

The Phase II trial, called HS14, was aimed to identify the optimal strength of Spherox by comparing three arms with different doses. There was no non-Spherox arm.

The Phase III compares Spherox with MF. This trial, which provides evidence for the modelling, is NCT01222559, now known as COWISI, but formerly called HS13. It is described in the submission as:
Phase III clinical trial designed to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product Spherox with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm^2

term aim of COWISI being to show superiority over MF. This is mentioned later, just after Table 14, where it is stated;

"The study was designed to test the non-inferiority and possible superiority of Spherox"

Results

Table 1 Results of COWISI trial

	Spherox	MF
Baseline KOOS	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
24 month KOOS	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
Change baseline to 24 months	Mean [redacted] Median [redacted]	Mean [redacted] Median [redacted]
Baseline MOCART	Not reported	Not reported
24-month MOCART	[redacted]	[redacted]

In the text below Table 16, we are told that the ANCOVA difference in change in KOOS is [redacted], which does not fit with the 24-month figures of [redacted]. Shortly below, we are told that ANOVA analysis gives figures of [redacted] for Spherox and [redacted] for MF, a difference of [redacted]

KOOS subscore results are given in Co-Don Table 17, [redacted], but with p values not given in the main Co-Don submission. [redacted]. Co-Don Table 18 gives changes from baseline in KOOS subscores, without p values, but reporting in the text that the improvement in one subscore, function in daily living [redacted] and median changes [redacted] for Spherox and MF respectively.

Since the [redacted], we do not think the subscore analysis adds anything of note.

The MOCART scores (Co-Don Table 20) at 24 months show [redacted]. MF gave slightly better results but the difference had confidence interval (presumably 95% CI, but not stated) of [redacted]. The submission notes (page 112 and table 29) that there was "at most - a very weak

The proportions of recruits improving by 10 or more points on the KOOS score ("responders") at 24 months were [redacted].

Overall, in the planned analysis, there was [redacted].

Once the results were available, an alternative analysis was carried out, using a one-sided confidence level of alpha = 0.05. [redacted]. The ERG is doubtful as to whether this post-hoc analysis with a changed alpha represents good practice.

In the alternative analysis, superiority was also reported for change in the physical functioning score of the IKDC current health assessment subscore, but no figures or p value were provided.

Additional analyses

The results for two age groups, 18-34 and 35-50 years, were compared. Both age groups are reported to have had significant improvements, but neither baseline KOOS scores or changes from baseline are not given in the main submission, only 24 month scores.

[redacted].

The Clinical.Trials.gov registration includes the outcome of days of absence from work (employment) and/or days of inability to follow usual activities during the last year or since the last visit, respectively, and time point when patient was back to work and/or to follow usual activities, but this is not reported in the submission.

Defect sizes

The COWISI trial included patients with (page 23 of Co-Don submission) defect sizes after debridement of >1 cm^2 to <4cm^2. The NICE ACI FAD recommends that ACI should be used only for lesions greater than 2cm^2. We therefore asked Co-Don as part of the clarification process, to split the COWISI results by defect size. We requested this breakdown because it is known that the effectiveness of microfracture declines as lesion size increases, and in our clarification request we hypothesised that the microfracture results in the smaller defects (<2 cm^2) might be better relative to Spherox, than in larger lesions. So the overall results of COWISI might have been missing a greater effect in the group to which the NICE FAD on ACI restricts it.

The results are in Table 5 – see row in bold. Figure 1 shows the flowchart for participants with lesion size >2cm^2. [redacted].

Study	Prospective, randomised, open-label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4–10 cm^2) with 3 different doses of Spherox in subjects with cartilage defects of the knee (Trial no. cod 16 HS 14)		
Study design	Dose-response study.		
Population	Males and females between ages of 18 and 50 years with an isolated single cartilage defect of the knee joint		
Intervention(s)	Spherox Group A:patients receiving 3-7 spheroids/cm^2 Group B:patients receiving 10-30 spheroids/cm^2 Group C: patients receiving 40-70 spheroids/cm^2		
Comparator(s)	Not applicable		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	No
Rationale for use/non-use in the model	Not used in the model as not comparison with microfracture that could be included in the network meta-analysis.		
Reported outcomes specified in the decision problem	Change of overall KOOS from baseline to final assessment at 12 months after implantation. Follow-up visits are planned at 24, 36-, 48- and 60-months.		
All other reported outcomes	• Changes in KOOS • MOCART (magnetic resonance observation of cartilage repair tissue) • Modified Lysholm score • IKDC (International Knee Documentation Committee) knee examination form • IKDC current health assessment form • IKDC subjective knee evaluation form • Bern score • International Cartilage Repair Society rating		

An unusual feature of this study, which has been published in part (Niemeyer et al 2016 [41]with the 12-month follow-up, Becher et al 2017 [40] with safety data) in that 63% of chondral defects were on the patella and only 37% on the femoral condyle. Patellar lesions tend to do less well than femoral condyle ones. Results are not provided separately for patella and condyle in the main submission. The trial appears to be well-designed, but for our purposes the lack of a control group reduces its value, and 30% withdrew prematurely. [redacted]. One entry criterion was defect size 4-10 cm^2 but the mean defect size was 5.6 cm^2 and only 10 of the 75 patients had 7-10 cm^2 defects.[40] The table of baseline characteristics gives no details of duration of injury or of previous attempts at repair. The groups were well-matched at baseline.

[redacted], especially in the high dose group, sometimes due to inadequate cell proliferation in culture. The rest include failure to attend visits or to complete data collection.

- *Spherox is shown to be more effective than MF across age categories studied.* ERG comment: Spherox was not shown to be more effective than MF.

- *Spherox can be used for large defects (up to 10 cm^2) whereas MF is generally used on smaller defects (1-4cm^2)* ERG comment: This comment is fair, because the larger the defect, the poorer the result with MF. However Co-Don did not provide any comparison with MF in defects larger than 4cm^2.

- *Spherox is associated with fewer serious adverse effects than MF.* ERG comment: There is a little support for this statement. In the Spherox arm of the COWISI trial there were no serious AEs related to the procedure. In the MF arm there were three AEs possibly related to the procedure, one deep vein thrombosis, one arthralgia and one adhesions.

- *Spherox may reduce the following complications because of the autologous cells used in the procedure:*
    - *Rejection and incompatibilities – where patients may require further procedures*
    - *Viral contaminations*
    - *Overcomes any objections to the procedure on religious grounds - no porcine derived collagen membrane*

ERG comment: none of these comments are relevant to a comparison to traditional MF, though the last might be if MF is used with a cap, or when Spherox is being compared with older forms of ACI. (Allografts were not included amongst the comparators.)

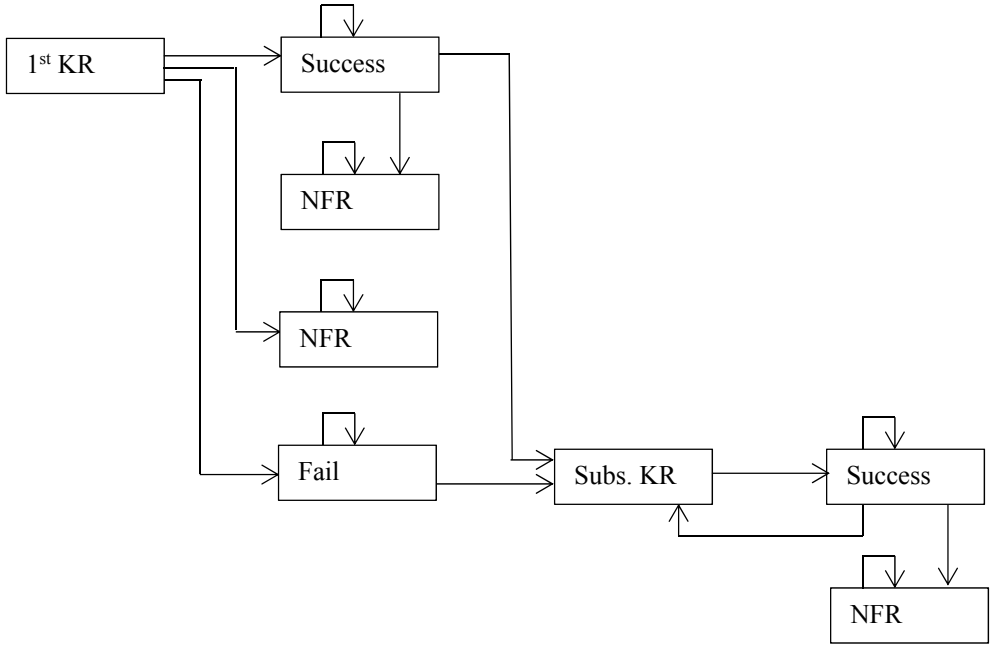
- *Using Spherox as first line surgical treatment before MF could be more effective than using MF 1st line before Spherox.* ERG comment: no evidence has been produced to support this statement because both the Cowisi and the Phase II trial excluded patients who had had previous MF. Based on research on other forms of ACI, we expect it to be true. However the FAD on ACI recommends ACI as first line in defects greater than 2 cm^2 so this comment is now superseded.

3.6 Clinical effectiveness - network meta-analysis

The ERG has appraised the methodology of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency. The NMA used only two outcomes, proportion of responders and failures (defined as requiring further surgery).

Baseline characteristics of included studies

Figure 1 Knee replacement module from age 55



4.2.3 Population

The starting age in the Co-Don model is 33 years. This reflects the baseline characteristics of the Phase III trial where the mean age at baseline of 37 years with 61% of male.

4.2.4 Interventions and comparators

There are four main interventions:

- Microfracture (MF)
- Spherox (SPHX)
- MACI (MACI)
- ChondroCelect (CC)

All of these interventions are modelled as being part of a possible sequence of two repairs. The 1st treatment is applied to all patients. The 2nd treatment is applied to those requiring repairs after having received the 1st treatment. The 10 sequences that are compared are:

- Microfracture followed by another treatment:
    - MF->MF
    - MF->SPHX
    - MF->MACI
    - MF->CC

4.2.8 Resources and costs

The resource use and many of the unit costs within the submission are taken from Mistry et al. With the exception of cell costs, the unit costs taken from Mistry et al are in 2012/13 prices and so are inflated by 3.4% to be in 2015-16 prices. These costs in Mistry et al are sourced from Clar et al 2005[58] and inflated from 2013-12 prices.

A company assumption is that Spherox implantation is done arthroscopically so requires a less invasive and shorter implantation procedure than other ACIs and so only incurs costs of £734 for both harvesting and implantation. The balance between total knee replacements and partial knee replacements is assumed to be 50:50 for 1st knee replacements, with all subsequent knee replacements being total knee replacements.

Unit costs of visits are taken from NHS reference costs. Unit costs of knee replacements are taken from the 2016-17 National Prices and Tariff.

Table 2 Unit costs

	Cost	Source
Harvesting	£734	Mistry et al, Arthroscopy, Table 22, inflated
Implanting SPHX	£734	Mistry et al, Arthroscopy, Table 22, inflated
Implanting CC and MACI	£1,065	Mistry et al, Arthrotomy, Table 22, inflated
Procedure MF	£3,122	Mistry et al, Procedure, Table 22, inflated
1st knee replacement	£5,566	2015-16 National Tariff
2nd knee replacement	£13,396	Mistry et al, 2nd TKR, Table 22, inflated
Outpatient visit	£121	Ref Cost: WF01A: OP: NA: FF: CL
Rehabilitation visit	£345	Ref Cost: REHBL2: rehabilitation for joint replacement

This, coupled with the cell costs and the visit and rehabilitation schedule of Mistry et al, results in the following total costs.

Table 3 Total costs of procedures

	SPHR	CHON	MACI	MFRC	1st KR	Subs KR
Cost of cells	£10,000	£16,000	£16,000	..	..	..
Harvesting	£734	£734	£734	..	..	..
Implantation	£734	£1,065	£1,065	..	..	..
Procedure	..	..	..	£3,122	£5,566	£13,397
Procedure cost	£11,468	£17,799	£17,799	£3,122	£5,566	£13,397
OP	6	6	6	3	2	2
Rehabilitation	3	3	3	3	0	0

MF->MACI	15.849	£8,170	15.849	£8,168
SPHX->MF	17.971	£14,184	17.971	£14,182
SPHX->SPHX	17.972	£15,018	17.972	£15,017
MACI->MF	18.117	£20,546	18.117	£20,544
CC->MF	18.110	£20,590	18.110	£20,588
MACI->MACI	18.116	£22,092	18.116	£22,091
CC->CC	18.109	£22,283	18.109	£22,283

4.3.2 Data Inputs: Correspondence between written submission and sources cited

Clinical effectiveness

A variety of clinical inputs are derived from Mistry et al. The following elements cross check:

- The 1.25% 2 yearly ongoing probability of moving from a successful ACI 1st repair to a 2nd repair.
- All the probabilities associated with knee replacement.

There is slight divergence between:

- There is slight divergence between: the 3.44% 2 year probability of moving from a successful microfracture 1st repair to a 2nd repair of the company model as derived from the company NMA and trial data which implies an annual probability of 1.73%, and the 1.61% estimate Mistry et al derive from Saris et al.[39]

Quality of life

The quality of life values applied by the company for repairs cross check with those of Mistry et al, including the assumptions that:

- quality of life among microfracture 1st repair and 2nd repair successes for years 5+ after the repair declines to 0.654, and
- quality of life among ACI 2nd repair successes after a microfracture 1st repair for year 4 and years 5+ after repair declines to 0.789.

The quality of life values applied by the company for knee replacements do not entirely cross check with those of Mistry et al. In Mistry et al those with no further repair (NFR) had a common quality of life value of 0.691. The company revises these for most of the NFR health states to 0.557. This worsens the cost effectiveness of sequences that result in more knee replacements.

Table 4 Knee replacement quality of life values cross check

In response to a 2nd clarification the company states that: "*The original approach was an incorrect application of the NMA data*". The company provides a revised set of estimates. These derive the microfracture response rate from the NMA relative risk. The response rates for the individual treatments are derived by applying the trial specific odds ratios to the microfracture response rate. The relative risks of the company NMA are not used for this analysis. As a consequence the ERG only applies these values as a sensitivity analysis. The last row of the table below contains the relative risks that appear to be implied by these estimates as calculated by the ERG.

Table 5 Alternative company estimates of response probabilities

	SPHX	CC	MACI	MF
1st repair 2yr probability of response P_2	[redacted]	91.59%	92.28%	78.44%
Source	NMA + OR from trial			NMA
Relative risks implied by 2yr probabilities of response P_2/Sphx(P_2)	1.000	1.152	1.161	0.987

The relative risks implied by the company revised estimates still appear to be different from the central estimates of figure 12 of the company submission and biased in favour of Spherox relative to MACI and ChondroCelect. The stated sources are also peculiar with the trials' odds ratios apparently being applied to the NMA.

Application of the NMA relative risks of failure

The same considerations around the application of the NMA relative risks of failure as outlined above for the NMA relative risks of response apply. The company has applied these to rates rather than to probabilities. This is relatively minor due to the low probabilities of failure.

The ERG revises the model to apply the NMA relative risks of failure to the failure probability for Spherox as inputted to the NMA.

2 year probabilities of response for 2nd repairs

For 2nd repairs the probability of response is calculated as the square root of the 2 year probability of response. The intention here appears to have been that this should be compounded over 2 model cycles and so after 2 annual cycles result in the 2 year probability of response. But in the model every incident patient that gets a 2nd repair has this 2nd repair probability of response applied only once. This causes the model to overestimate the initial proportion of patients achieving successes and seems

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of **30 October** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8 of the ERG report states: This means that the NICE scope issued for this STA is out of date, and microfracture is no longer a comparator for defects over 2 cm^2. The key comparators are now other forms of ACI, though there are problems with the availability of these, as reported later. So the decision problem as defined by Co-Don is also out of date – the timing was unfortunate." Issuance of the FAD from TA 477 does not render the scope for this STA, and specifically its inclusion of MF, out of date or irrelevant. Indeed, MF was not appraised within TA477 and so could not be recommended or otherwise.	Please remove the entire paragraph in question.	There is no guidance from NICE suggesting that MF is no longer a relevant comparator.	The NICE FAD from the appraisal of ACI clearly implies that ACI should be a primary procedure, and states: "The consensus among UK clinicians is that ACI is the only effective treatment option for defects that are over 2 cm_2 when symptoms persist after non-surgical management." So the ERG view is that the comparator (for lesions >2cm^2 should be other forms of ACI. The comment that "MF was not appraised within TA477" is not quite correct. It was not formally appraised, in the sense that NICE did not issue a scope for an appraisal of

			MF (indeed, it has never been appraised by the Technology Assessment Programme) but we examined the accumulating evidence for MF and concluded that it was not a satisfactory long-term treatment for chondral defects.

Issue 2 Confidential data on drop-out rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
One page 10 the ERG does not mark the value of [redacted] as academic in confidence, contained within the sentence: "Although the Phase II dosage study was of reasonable quality, apart from the [redacted] drop-out rates due to protocol violations…"	This data of [redacted] should be marked as academic in confidence.	This data is confidential.	Accepted, our mistake.

Issue 3 Clinical effectiveness from original submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 12: "The company accepts that all the clinical effectiveness estimates for the model of its original submission are wrong and biased in favour of Spherox."	The Company thinks this statement should be replaced with the following statement: "The company accept that the KOOS response parameter in the model was implemented incorrectly."	This statement is incorrect. The Company only stated that the original approach to applying the NMA results was incorrect not that all the clinical effectiveness estimates were wrong or that they were biased in favour of Spherox.	The revised company estimates for response are less optimistic for Spherox which implies that the company accepts that the original ones were wrong and biased in favour of Spherox. The text might better read: "The company accepts that all the main response clinical effectiveness estimates for the model of its original submission were wrong and biased in favour of Spherox"

Issue 4 Confidential information on trial outcome

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 13 of the ERG report, the ERG has not marked confidential information as confidential.	Protect academic in confidence information. Please reword to: "[redacted]	This trial result should be marked as academic in confidence, as it relates to the two year trial results.	The wording looks identical. The CHMP report from the EMA gives the 12

This relates to the following sentence: “[redacted] [redacted]”	[redacted]”		month results from COWISI. We accept that the 24 month overall result should be AiC.

Issue 5 Cartilage cultivation time

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on Page 18: Chondrocytes are harvested from healthy articular cartilage, cultivated for 8-10 weeks in the laboratory. This statement is factually incorrect, as the process in fact takes about 6-8 weeks – as detailed on page 23 of the Spherox SmPC.	Amend sentence to “…cultivated for 6-8 weeks in the laboratory.”	To accurately state the cultivation time	Accepted but unimportant.

Issue 6 Licensing - spheroids of human autologous matrix-associated chondrocytes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 of ERG report states: “Spheroids of human	Add sentence: “In addition, Spherox has an EMA license for treatment of the	To accurately state the licensing status.	The statement is correct so this is not a factual

autologous matrix-associated chondrocytes are licensed in Germany for the treatment of articular cartilage defects of the knee, hip, shoulder, elbow and ankle." This statement is incomplete, as an EMA MA license covering Europe for the treatment of the knee is in place as well.	knee cartilage."		inaccuracy. The EMA licence is mentioned elsewhere.

Issue 7 Target population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 of the ERG report states: The EMA approval mentions adults and symptoms. In context, there is a lack of clarity on the treatment this sentence refers to.	Please amend sentence to: "The Spherox EMA approval mentions adults and symptoms."	To avoid misunderstanding and clearly state the treatment being referred to.	No response required

Issue 8 European license of ACI treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 of the ERG report states: So the key comparators are the other forms of ACI, and in particular Vericel's MACI, because it has the only licence in Europe, albeit temporarily suspended. This statement is both inaccurate and misleading. In fact, Spherox is the only ACI treatment with an active licence in Europe.	Please replace ", and in particular Vericel's MACI, because it has the only licence in Europe, albeit temporarily suspended." With ", although neither ACI has an active license in Europe." Please also add following sentence: "That said, Spherox currently is the only ACI treatment with an active licence in Europe."	To correctly state the licensing status of ACI treatments in Europe.	No revision required because "temporarily suspended" is correct.

Issue 9 Prior ACI use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 of the ERG report states: "The NICE guidance of 2004 recommended ACI only in research, and the 2015 ACD repeated that	The statement that "So very little ACI has been done" should be removed.	This statement is not a fact and is not supported with evidence.	It is a fact, as evidenced by our clinical colleagues. To refute this comment, Co-Don would have to

recommendation. So very little ACI has been done."			provide data on numbers of ACI procedures in the NHS.

Issue 10 Licensing status of Vericel MACI

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24: The licence for Vericel MACI is currently suspended because they have no European production facility, but may be reinstated after the EMA has inspected the production site in the USA. We do not know if Vericel will open a new facility in Europe. To our knowledge there are no clearly established facts to support this statement. To avoid ambiguity, the sentence should be amended to represent the facts.	Please amend section to: "The licence for Vericel MACI is currently suspended. Spherox currently is the only ACI treatment in Europe that is available and has an active license."	To clearly state which ACI treatments have an active license in Europe and are available for patients.	No factual inaccuracy. We are aware that Vericel have written to NICE about the licence situation.

Issue 11 Account of current provision of ACI in the UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 23: "The submission does not give an account of current provision of ACI in the UK"	The Company thinks this statement should be replaced with the following statement: "The submission does not give a full account of current provision of ACI in the UK."	This is not entirely correct. The Company notes in the submission the 2005 decision and the new guidance and stated that due to access to ACI issues, MF is likely to be the most common procedure. In clarification response, we made it clear our position on traditional ACIs so reference here would be appropriate.	No response required. We note the Co-Don response to clarification question 1, which was from NICE, not the ERG.

Issue 12 Clinical procedure assumption

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26, the ERG report states: "……cell viability and speed better when ACI is done by mini-arthrotomy than arthroscopically."	The Company thinks the following statement should be removed: "However MACI can also be done by mini-arthrotomy. (And arthroscopically, but cell viability and speed are better when ACI is done by mini-arthrotomy than arthroscopically.36" The Company thinks this statement should be replaced with the following	The sentence is incorrect. Spherox 2nd Stage cell implantation does not require a scaffold/implant device like other ACI/MACIs and therefore no handling or manipulation of cells on a scaffold/implant. Further Spherox was not included in this study.	No factual inaccuracy. The statement is correct and referenced. MACI can be done by mini-arthrotomy. We have stated in the ERG report that Spherox can be done arthroscopically.

	statement: "MACI, where a scaffold for implantation is required for 2nd stage implantation (as required by VeriMaci and ChondroCelect) can also be performed arthroscopically but cell viability and speed are less effective that with ACI performed via a mini-arthrotomy due to handling and manipulation of the cell ceded scaffold for implantation 36. However, this does not apply to Spherox as there is no scaffold required for implantation and was not included in this study."		

Issue 13 Timing of Spherox clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26, the ERG report states "The phase II RCT was conducted prior to the phase III and aimed to identify the optimal strength of Spherox by comparing three arms with different doses."	The Company thinks the following statement should be removed: "…was conducted prior to the phase III"	The sentence is incorrect. Both trials started simultaneously in 2010, but a faster recruitment in phase II (2 years of recruitment) resulted in earlier results being available for the phase II study (current 4 years data). Patients for phase III were recruited until the end of 2014,	Accepted.

		therefore 24 months results were available so far.	
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
On page 26, the ERG report states “The phase II RCT was conducted prior to the phase III and aimed to identify the optimal strength of Spherox by comparing three arms with different doses.”	The Company thinks the following statement should be removed: “…was conducted prior to the phase III”	The sentence is incorrect. Both trials started simultaneously in 2010, but a faster recruitment in phase II (2 years of recruitment) resulted in earlier results being available for the phase II study (current 4 years data). Patients for phase III were recruited until the end of 2014, therefore 24 months results were available so far.	Repetition of point above.

Issue 14 COWISI trial exclusion criteria

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
On page 27, the ERG report states: “The exclusion criteria in Table 5 also list radiological signs of OA as an exclusion but according to Table 8, four people with OA were included.”	This statement should be removed.	The CSR provides the criteria for defining - it's not that the trial included patients it was meant to, rather it excluded specific types of OA and that the 4 OA patients included were outside of those criteria. This statement implies there	Table 5 of the Co-Don submissions says under exclusion criteria: “Radiological signs of osteoarthritis”. There is no mention of “specific types of OA”.

		is a discrepancy and is therefore incorrect.	No change required.

Issue 15 Incomplete academic in confidence marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 30 the ERG report does not completely mark the value of [redacted] as academic in confidence contained within the following sentence: "Shortly below, we are told that ANOVA analysis gives figures of [redacted] for Spherox and [redacted] for MF, a difference of [redacted]"	The Company thinks the value of [redacted] should be fully marked yellow.	This information is confidential and should be fully marked.	Accepted. Apologies for that.

Issue 16 Provision of p values for KOOS subscore results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 30, the ERG report states: "KOOS subscore results are given in Co-Don Table 17, with the Spherox results better for all subscores, but with p values	Please remove "but with p values not given" from this sentence.	It is incorrect to say these p values were not provided. These p values were provided to the ERG as part of the CSR appendices.	The p values were not provided in the main Co-Don submission.

not given.”			

Issue 17 Provision of baseline KOOS values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 32, the ERG report states: “The results for two age groups, 18-34 and 35-50 years, were compared. Both age groups are reported to have had significant improvements, but neither baseline KOOS scores or changes from baseline are not given, only 24 month scores.” Baseline KOOS values and changes from baseline were, however, analysed and presented in the appendices of the CSR.	The statement “, but neither baseline KOOS scores or changes from baseline are not given, only 24 month scores” should be removed from the sentence.	To correctly acknowledge the availability and presentation of the mentioned data in the company submission.	The data were not provided in the Co-don submission. We received a profusion of appendices, some rather long. All important data should be in the main submission.

Issue 18 Failure rates and NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on	The Company thinks this statement	This is not clear and implies	The Co-Don submission

page 35: “Co-Don explained how they had calculated failure rates in the NMA, when there were no failures in COWIS and SUMMIT”. This is not clear and implies that the Company state there were no failures reported in COWISI trial, whereas there were [redacted] in the MF arm.	should be replaced with the following statement: “Co.Don explained how they handled failure rates in the NMA when there were no failures in the Spherox arm of the COWISI trial resulting in a [redacted] data point”	that the Company state there were no failures reported in COWISI trial, which would be incorrect.	states “no failures were observed in COWISI” (page 79). In clarification responses, Co-Don explained that because no failures were seen, an assumption was made that in each arm 0.5 patients experienced failure.

Issue 19 Provision of patellar and femoral subgroup results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 36, the ERG report states: “Patellar lesions tend to do less well than femoral condyle ones. Results are not provided separately for patella and condyle.” Baseline and follow up visit KOOS values for femur and patella lesions were, however, provided in the appendices of the CSR.	The sentence “Results are not provided separately for patella and condyle.” should be removed from the report.	To correctly acknowledge the availability and presentation of the mentioned data in the company submission.	Data not included in the main company submission. Note that in the COWISI trial, all defects in the Spherox group were on the femur (Table 7 of Co-Don submission).

Issue 20 Patients remaining in phase II study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 36, the ERG report states: "By the 4-year follow-up only [redacted] of the original 75 remained." In fact, [redacted] patients remained in the study, [redacted] patients of which were included in the per protocol population. This difference is due to major protocol deviations rather than withdrawal.	Replace "[redacted]" with "[redacted]" in this sentence.	It is incorrect to say that only 33 of the original 75 remained in the study.	Accepted. Figure 4 of the Co-Don submission shows that only [redacted] were protocol compliant. But the ITT population was 73. The source of the value of [redacted] is unclear. The ERG agree to replace the sentence to "By the 4-year follow-up only [redacted] of the original 75 remained protocol compliant."

Issue 21 Duration of injury

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 37, the ERG report states: "No analysis by duration of defect, or by history of previous repair attempts, was reported, but at clarification stage, Co-Don provided data showing no difference by duration of	Refer to "duration of injury" rather than defect, as per ERG Clarification question and response.	To keep the terminology consistent with that used during the appraisal.	No response required

injury." However, sentence should "duration of injury" rather than defect.			

Issue 22 KOOS score and primary outcome

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 38: "KOOS is not used, despite being the primary outcome in the COWISI trial."	The Company thinks this statement should be removed completely.	This is statement is incorrect. The KOOS from COWISI is used to derive the proportion of responders outcome, which is used in the NMA and model. A responder is defined a patient having a 10-point improvement in KOOS score from baseline.	Fair point. What we had in mind was analysis using actual KOOS scores, since using the cut-off of 10 may conceal some with, say, 11 and others with much greater improvements.

Issue 23 Concomitant surgery

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in Table 7 (page 41) that for concomitant surgery for COWISI it is "? none".	This should be reported as "0" or just "none".	It is incorrect to indicate that this data point is uncertain, as these data were provided in the CSR and ERG clarification response.	Accepted – we didn't correct the draft figure.

Issue 24 Model structure schematic

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The model schematics in Figure 2 and Figure 3 (pages 52 and 54) show a "Fail" health state. This is not an actual health state included in the model.	The schematics should revised by removing the "Fail" health state.	These are not health states in the model and should be removed so as not to imply that they exist.	We know that, but people don't have second procedures unless they have failed, so we think the figure explains that. The text before ERG figure 2 correctly describes the model.

Issue 25 TA 477 typo

Description of problem	Description of proposed amendment	Justification for amendment
On several occasions TA477 is written as TA447. This occurs on the following pages: • Pages 49, 59, 65, 69, 80	This should read as "TA477"	These are typos.

Issue 26 Transition from successful first repair

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report makes several incorrect statements regarding how patients can transition from the	The Company think this should be revised to state the following on each page: • Page 53: ""In the company model	This is incorrect. Patients in the Successful First Repair state can also remain in that health state in addition to	The key word here is transition. In the company model, only one transition is possible – to 2nd

Successful 1st repair state. These are shown below: • Page 53: "In the company model 1st repair successes can only transition to 2nd repairs." • Page 70: "Successes from a 1st repair cannot lose response and move into the NFR health state. To the age of 55 they can only exit to a 2nd repair."	1st repair successes can only transition to 2nd repairs or remain in the successful 1st repair state." • Page 70: "Successes from a 1st repair cannot lose response and move into the NFR health state. To the age of 55 they can only exit to a 2nd repair or remain in a successful first repair state."	moving to 2nd repair.	repairs. We think there should be another option to lack of success but no further repair. The proposed company revision is factually correct but in the opinion of the ERG the ERG description and model schematic is sufficiently clear on this.

Issue 27 Quality of Life for Knee Replacement "No further repair" states

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The ERG makes several incorrect statements in the ERG report related to the utility attributed to the "No further repair" health state following Knee Replacement. These are outlined below: • Page 53: "Note that this	These statements on pages 53, 67, and 69 should be removed or revised to not say that there are different utilities for different NFR states. Table 13 and Table 22 should be revised to have the following health states and utilities:	This is incorrect. If you have a successful 1st KR then move to NFR your utility is 0.691 i.e. AW19 in TP sheets. If your 1st KR fails and you move to NFR your utility is also 0.691 i.e. AT19 and AU19 in TP sheets. Further NFR from KR is captured in	The ERG report is based on the first model submitted by the company. This is because a number of the model revisions and clinical input revisions of the company are undocumented and

NFR health state differs from the NFR health state of those moving directly from their 1st KR to NFR without success and is associated with a different quality of life." • Table 13 and Table 22: Quality of life values for knee replacements • Page: 67: The ERG report states that for quality of life values for knee replacement - "The company revises these for most of the NFR health states to 0.557." • Page 69: The ERG report states that - "Those moving to NFR from a 1st KR success, immediately from a subsequent KR, and from a subsequent KR success have a quality of life of 0.557 applied.	• NFR from 1st KR - 0.691 • NFR from 1st KR success - 0.691 • NFR from failed further KR – 0.691 • NFR from successful further KR – 0.691	column BD (i.e. utility in BD19). At the time of the original submission, there was one value that was 0.557 and this was corrected following the first ERG clarification questions (column AW in each Markov model treatment arm).	appear incorrect. Tables 13 and 22 (reproduced below) appear to be consistent with the originally submitted company model, the model columns the values relate to being shown below. The values the company appears to disagree with appear to the ERG to relate to columns BD and BE of the company markov sheets.

Table 13. Knee replacement QoL Health state	QoL

1st KR (Cols AB:AE)	0.615
Subs KR (Cols AR, AS, AV)	0.557
Success (Cols AP, AQ, BC)	0.780
NFR from 1st KR (Cols AT, AU)	0.691
NFR from 1st KR success (Col AW)	0.557
NFR from 2nd KR (Col BD)	0.557
NFR from 2nd KR success (Col BE)	0.557

Table 22. Knee replacement QoL cross check

	QoL	
Health state	Company	Mistry et al
1st KR (Cols AB:AE)	0.615	0.615
Subs KR (Cols AR, AS, AV)	0.557	0.557
Success (Cols AP, AQ, BC)	0.780	0.780
NFR from 1st KR (Cols AT, AU)	0.691	0.691
NFR from 1st KR success (Col AW)	0.557	0.691
NFR from 2nd KR (Col BD)	0.557	0.691
NFR from 2nd KR success (Col BE)	0.557	0.691

Issue 28 Starting age in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 54: “The patient population reflects the baseline characteristics of the Phase III trial with a	The Company thinks this statement should be replaced with the following: “The patient population had a starting age of 33 years and was 60% male.”	This is incorrect. The starting age in the model was 33 and this was not based on the COWISI population.	The starting age in the MTA and the Co-don model is 33 years.

mean age at baseline of 34 years".			

Issue 29 Unit cost of first knee replacement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In table 14 on page 60 the ERG report the cost as "£5,556" for "First knee replacement". This is not the unit cost.	This should be revised to "£5,566".	This is not the correct unit cost.	This is a typo and the ERG accepts that the cost should be reported as £5,566 and not as £5,556

Issue 30 Correspondence between written submission and sources cited

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on page 67: "There is slight divergence between: the 3.44% 2 year probability of moving from a successful microfracture 1st repair to a 2nd repair of the company model which implies an annual probability of 1.73%, and the 1.61% estimate Mistry et al derive	This statement should be revised so as to not imply that this value was taken or derived from either Mistry et al. or Saris et al.	This statement incorrectly implies that the calculated values of 3.44% and 1.73% are not taken or derived from Mistry et al. or Saris et al. There is no issue of a discrepancy because it is not related to any data taken from these publications, rather it is related to the NMA data.	The ERG has revised as following: "There is slight divergence between: the 3.44% 2 year probability of moving from a successful microfracture 1st repair to a 2nd repair of the company model as derived from the company NMA and trial data which implies an annual probability of 1.73%, and the 1.61%

from Saris et al.”			estimate Mistry et al derive from Saris et al”

Issue 31 Correcting annual probability for second repair of MF

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on page 67: “The 3.44% 2 year probability of moving from a successful microfracture 1st repair to a 2nd repair of the model which implies an annual probability of 1.73%”	This should be changed from “1.73%” to “1.72%” to reflect the correct model data.	The value of 1.73% was not used in the model. The value was 1.72%.	The ERG probability is in line with the company method for converting 2 year failure rates to 1 year failure rates elsewhere = 1-sqrt(1-3.44%). For reasons that are unclear the company simply halves 3.44% to get 1.72%. The implication is that the model data is slightly incorrect.

Issue 32 Alternative ERG application of the NMA relative risks of response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG reports response rates calculated using an alternative ERG application	Using the mean MF rate of the trials of 69.59%, we derive the following:	Data incorrect	These calculations are in the ERG amended model Clinical Inputs

of the NMA relative risks of response (Table 24, page 71). These data do not match what the Company calculates in the last row for: ERG 1st repair 2yr probability of response P2 with MF = 69.59%	• For MF: 69.88% - if simple average of 79.6%, 68.1%, and 62.0% If using 69.59% for MF rate, however, we calculate the following: • Spherox: [redacted] • MACI: 87.88% = 0.7189 x 1.223		worksheet. The pooling is not an average of the three trials but the sum of responders (119) divided by those in the MF arms (171). There are minor discrepancies because the ERG has used the MF percentage not rounded to 2 decimal places hence [redacted] for Spherox and 87.89% for MACI. These are as per table 24 of the ERG report and are minimally different from the values proposed by the company.

Issue 33 Incorrect spelling of ChondroCelect

Description of problem	Description of proposed amendment	Justification for amendment
Page 71: ChondroCelect is spelled “ChonderoCelect”	The spelling should be corrected.	The spelling is incorrect.

Issue 34 Revised calculations submitted to ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on page 72 that information regarding calculations was not submitted. For example: • "The company supplies an alternative set of estimates and sources, but does not outline the arithmetic of these estimates." • In the absence of further information (requested 10th October) about the revised company calculations the ERG will only apply these in a sensitivity analysis	These statements should be removed.	This information was provided as part of the ERG responses.	The company is correct that it has provided further clarification of its revised method. The company provides a revised set of estimates. These derive the microfracture response rate from the NMA relative risk. The response rates for the individual treatments are derived by applying the trial specific odds ratios to the microfracture response rate. The relative risks of the company NMA are not used for this analysis. As a consequence the ERG only applies these values as a sensitivity analysis.

Issue 35 Registry enrolment of UK patients using Spherox

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88: We note that the ICRS has set up a registry for long-term follow-up of ACI and other knee procedures, and if Spherox is approved (now or later), it could be under condition that patients are registered with ICRS so that long-term data will accrue. This statement is incorrect as this commitment already applies for UK usage of Spherox.	Please amend to: "…it will be under the condition that…"	To correctly state the commitment for UK usage of Spherox.	We were not informed of this commitment. But we welcome it. However, this is not a factual error.