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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Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/69/10.
Competing interests of the authors: none.
Rider on responsibility for report. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be cited as;
Cummins E, Armoiry X, Metcalfe A, Royle P, Mistry H, Johnston R, Rodrigues J, Waugh N. Spherox for treatment of articular cartilage defects in the knee. A Single Technology Appraisal. Warwick Evidence, 2017.

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.)

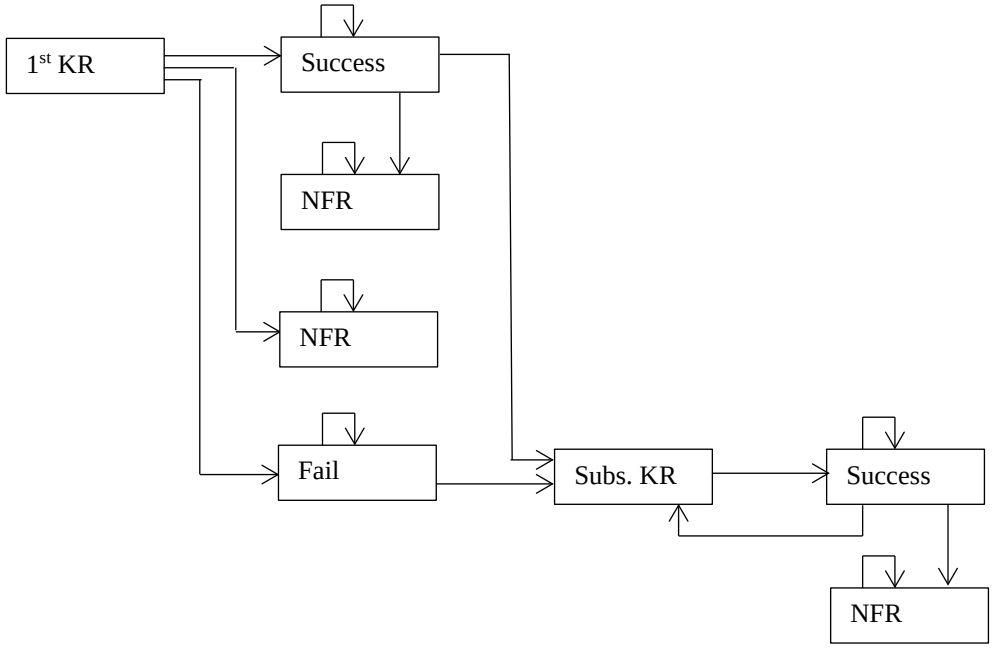
- *Using Spherox as first line surgical treatment before MF could be more effective than using MF 1st line before Spherox.* ERG comment: no evidence has been produced to support this statement because both the Cowisi and the Phase II trial excluded patients who had had previous MF. Based on research 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