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**Autologous chondrocyte implantation with Chondrosphere for treating
articular cartilage defects in the knee: An Evidence Review Group
perspective of a NICE Single Technology Appraisal**

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Short running header: **Chondrosphere for articular cartilage defects: an ERG perspective**

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Abstract

Chondrosphere (Spherox) is a form of autologous chondrocyte implantation (ACI). It is licensed for repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee with defect sizes up to 10 cm² in adults. In a single technology appraisal (STA) [TA508] undertaken by the National Institute of Health and Care Excellence (NICE), Warwick Evidence was the Evidence Review Group (ERG) invited to independently review the evidence submitted by the manufacturer, Co.Don. The clinical effectiveness data came from their COWISI randomized controlled trial (RCT) which compared Chondrosphere with microfracture (MF). The timing of this appraisal was unfortunate given that MF was no longer the most relevant comparator because NICE had contemporaneously published, guidance approving ACI in place of MF. Moreover, the COWISI RCT enrolled mostly patients with small defect sizes. Evidence of clinical effectiveness for Chondrosphere used in people with larger defect size came from another RCT which compared three doses of Chondrosphere, and that by design could not provide evidence comparing Chondrosphere to any other forms of ACI. To estimate the relative clinical performance of Chondrosphere versus other ACI, Co.Don conducted an indirect treatment comparison by network meta-analyses (NMA). The NMA was flawed in that the distribution of population characteristics that are effect modifiers greatly differed across the treatment comparisons of the network. The ERG questioned both the appropriateness of the NMA, and the validity of the resulting estimates. Co.Don estimated the cost-effectiveness of Chondrosphere using a lifetime Markov model with all patients receiving the first repair during the first cycle of the model then moving into one of three health states: success, no further repair (NFR), or a second repair, if necessary. Subsequent to the first cycle those who were a success either remained a success or moved to second repair. All those in NFR remained in NFR. The cost-effectiveness of Chondrosphere compared to other ACI forms relied on the clinical effectiveness estimates of success and failure rates obtained from the company's indirect comparisons, the validity of which the ERG questioned. The company revised cost-effectiveness estimates for Chondrosphere versus MF, and for Chondrosphere versus matrix-applied characterised autologous cultured chondrocyte implant (MACI) were £4,360 and around £18,000 per quality-adjusted life year (QALY) gained, respectively. NICE recommended ACI using Chondrosphere for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee in adults, only if certain requirements were met.

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Key points for decision makers:

- The main source of evidence for Chondrosphere came from the COWISI randomised controlled trial (RCT) which was deemed of good quality, though blinding of intervention was impractical, duration of patient follow-up is as yet only two years, and it included patients with defects smaller size ($<2\text{cm}^2$) than NICE currently approves for ACI. The results suggested that Chondrosphere is clinically effective, and the improvement lasts for at least four years in patients with large defect size (up to 10 cm^2).
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- No reliable comparative evidence is available to gauge the benefit of Chondrosphere against other forms of ACI.
- In the absence of a head-to-head trial, indirect treatment comparisons using network meta-analysis (NMA) methods can be explored. However, in the present case the heterogeneity of included studies was so large that the transitivity assumption does not hold, and it is preferable not to undertake any NMA.
- NICE has recommended ACI using Chondrosphere as an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV) in adults, only if: 1) the person has not had previous surgery to repair articular cartilage defects; 2) 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) and 3) the defect is over 2cm^2 .

1. Introduction

The National Institute for Health Care and Excellence (NICE) is an independent body responsible for appraising licensed medical interventions and issuing guidance on their use within the UK National Health Service (NHS). In recent years, NICE has assessed many new pharmaceutical products through the single technology appraisals (STA) programme in which the manufacturer of a particular technology submits evidence on the clinical and cost-effective use of its product for a single indication.

The HTA Programme commissioned Warwick Evidence to be the Evidence Review Group (ERG) to critique the clinical and economic evidence submitted by the manufacturer Co-Don. This paper summarises the ERG's critique of Co-Don's submission to NICE and provides a brief summary of the development of NICE guidance.

2. ERG critique of the Decision Problem defined by the company

Loss of articular cartilage, also referred to as a chondral defect, 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. The most common symptom of a chondral defect is pain. Other symptoms include temporary locking of the knee in one position, and swelling. The longer-term consequence of chondral injury is osteoarthritis (OA), which develops over time and often leads to a need for knee replacement. The severity of cartilage damage can be graded according to an international scoring system which is mainly based on the depth of lesions[1]: in the lowest grade, patients only present soft indentation and/or superficial cracks, while in the highest grade patients have defects of the full thickness of cartilage involving the sub-chondral bone.

The final scope issued by NICE in June 2017 [2], suggested that there are several possible interventions for symptomatic patients with chondral injury. One option is best supportive care whereby patients do not undergo any operative interventions and use symptomatic relief, with or without physiotherapy. The scope suggested that operative interventions are: 1) lavage and debridement; 2) 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 (unlike hyaline cartilage, which is more predominantly type 2 collagen); 3) mosaicplasty which involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area; and 4) autologous chondrocyte implantation (ACI) in which a piece of articular cartilage is taken from

the knee and the cartilage-producing cells, called chondrocytes are cultured and multiplied in the laboratory and then implanted into the chondral defect.

At the time Co.Don presented a submission to NICE for Chondrosphere, which is a fourth generation of ACI, earlier generations of ACI were being appraised as part of the TA477 multiple technology appraisal (MTA). Some of the NICE comparators, such as debridement and lavage, and mosaicplasty, were deemed inappropriate by the Company. The ERG concurred. Evidence for MF came from the company's Chondrosphere dose ranging study and an RCT comparing Chondrosphere versus MF. However, the final appraisal document (FAD) for the ACI MTA [3], which was released after the Chondrosphere appraisal had started, concluded that MF was no longer a relevant comparator to ACI for defects over 2cm², so that alternative forms of ACI became the recommended options for symptomatic patients. Final guidance on ACI was issued in October 2017 [4].

ACI has been used since at least 1987 [5] but the procedure has evolved over time with different ways of implanting the chondrocytes into the chondral defect.

Three comparator ACIs were considered by NICE in the MTA: 1) ChondroCelect which is a form of ACI in which the cultured cells are combined with a biodegradable collagen I/III patch, with characterised chondrocytes; 2) the Matrix ACI system (MACI – short for “matrix applied characterised autologous cultured chondrocyte implant”) which consists of a matrix of collagen membrane into which the chondrocytes are loaded at operation; and 3) 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, which has cultured and provided autologous chondrocytes (OsCells) for use in ACI since 1997.

Although ACI was recommended by NICE by the time of the Chondrosphere appraisal, there were problems with availability for the three forms appraised in the MTA. ChondroCelect, which received European marketing authorisation in October 2009 [6] is no longer on the market and production has ceased. MACI, which was approved in Europe in June 2013 [7], was also not available as of October 2017 because of the absence of any manufacturing facility in Europe, which led the EMA to suspend their European license. Lastly, the Oswestry facility is authorised to produce cells only for use in the RJAH Hospital in Oswestry. The hospital accepts referrals from elsewhere but capacity is limited. ACI was therefore not available in the UK in any form outside of the research setting.

The Co.Don submission aimed to compare the clinical and cost-effectiveness of Chondrosphere to that of MF and other forms of ACI.

Chondrosphere (Spherox) is a form of fourth generation ACI. Chondrocytes are harvested from healthy articular cartilage, cultivated for 6-8 weeks in the laboratory, and condensed into spheroids (chondrospheres) of cells which are then implanted into the defect. Spherox is licensed in Germany for the treatment of articular cartilage defects of the knee, hip, shoulder, elbow and ankle. Spherox received a marketing authorisation from the European Medicines Agency (EMA) [8] in July 2017 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 cm² in adults.

3. Company's original submission and outcome following appraisal committee.

3.1. Submitted Clinical Evidence and ERG critique

Co-Don have been unfortunate in the timing of the Chondrosphere appraisal. They have based their submission largely on their single randomized controlled trial (RCT) which compared Chondrosphere with MF. However, NICE has approved ACI in place of most MF[4]. So the key comparators are the other forms of ACI, albeit not currently available in the UK.

3.1.1. Evidence from head-to-head comparisons

The Co-Don main submission presented the results from two trials, one Phase II and the other Phase III. The ERG found no other trials but did find a number of case series. No other systematic reviews of Chondrosphere were found.

The Phase II trial, called HS14 (NCT01225575), aimed to identify the optimal dose of Chondrosphere by comparing three arms with different doses (3-7 spheroids/cm², 10-30 spheroids/cm², or 40-70 spheroids/cm²). There was no non-Chondrosphere arm. This study included people with large defects (4-10cm²) with about two-thirds having patellar defects.

The ERG considered the dose ranging trial was well-designed and that the enrolled population matched the indication validated for ACI, especially with regards to defect size. However, the lack of a control group was deemed to reduce its value. Interim effectiveness results (at 12 months) together with safety data (at 36 months) have been published [9, 10] while final effectiveness and safety results (at four years) were presented in confidence by the Company. Four-year results showed no important difference amongst the three groups based on the Knee Injury and Osteoarthritis Score (KOOS) score which assesses pain, symptoms, activities of daily living, sport and recreational activities (on a scale of 0 to 100, where 100 is best). The key results of the Phase II RCT are that, in patients with large defects, the KOOS score improved from baseline to 24 months and that improvements seen at 24 months are sustained at four years.

The Phase III study, called COWISI for “*CO.DON Wirksamkeit and Sicherheit*” (NCT01222559), was the pivotal trial to support the approval of Chondrosphere. COWISI was a prospective, randomised, open label, multicentre Phase III clinical trial that compared Chondrosphere to MF in 102 patients with defect sizes between 1 and 4cm². The dose of spheroids depends on the size of the defect, the recommended dose is 10-70 spheroids/cm² defect. 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 will be evaluated with longer term follow-up durations (36, 48, 60 months) not available as of June 2018. The magnetic resonance observation of cartilage repair tissue (MOCART) score is based on imaging by MRI (magnetic resonance imaging). 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 results of the COWISI RCT at two years are not yet published and were provided in confidence by the Company as part of their submission to NICE.

Based on the Cochrane risk of bias score [11], the ERG considered that COWISI was a good quality trial though blinding of intervention was impractical because the Chondrosphere group had two procedures. The sample size was calculated to show non-inferiority of Chondrosphere against MF whereas other trials of ACI (SUMMIT, TIG/ACT, and ACTIVE) were designed to show if ACI was superior to MF.

The ERG felt that the main problem with the trial at the time of the appraisal was that results were only available to 24 months. Longer-term follow-up is planned, to five years. The sample size was based on showing non-inferiority which seemed odd. The ERG would have expected the trial to be aimed at showing that Chondrosphere 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 Chondrosphere 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. Similarly, 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 was no such justification in the Co-Don submission.

The KOOS scores improved from baseline to 24 months with both Chondrosphere and MF. The repeated-measures ANCOVA testing for non-inferiority of Chondrosphere against MF were presented by the Company in confidence as were the results based on the MOCART scores at 24 months.

At clarification stage, the ERG requested results from the COWISI RCT by defect size given that this trial included patients with defect sizes of $>1 \text{ cm}^2$ to $<4\text{cm}^2$ and that NICE ACI FAD recommended that ACI should be used only for lesions greater than 2cm^2 . However, no clear conclusion could be drawn based on these additional results given in particular the small number of patients per defect size category.

3.1.2.Evidence from indirect treatment comparisons or from other sources

The Co-Don submission presented indirect evidence for comparisons of Chondrosphere with two other forms of ACI, ChondroCelect and Vericel MACI, via a network meta-analysis (NMA). The network included three RCTs and used MF as a common comparator: COWISI, SUMMIT [12], and TIG/ACT [13, 14]. Two outcomes were assessed, responders and failures. The studies varied in how response was reported, with response 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.

The ERG identified several methodological flaws in the NMA, in particular focusing on the assumptions of homogeneity and similarity. Based on inspection of the baseline characteristics of the three RCTs (Table 1), together with the comparison of outcome definitions, the following major comments were made by the ERG:

- 1) The transitivity assumption does not hold, since the distributions of population characteristics that are effect modifiers differ across the treatment comparisons of the network. Three 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;
- 2) 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.
- 3) 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.

For these reasons the ERG did not think it was appropriate to do an NMA, and considered the validity of the results of the indirect comparisons to be very questionable.

Given the paucity of RCT data and the limitations of the NMA, the ERG looked to see if anything could be gleaned from case series.[15-19] However, these case series were mainly small, three were just pilot studies, two were available only as conference abstracts, and others have duration of only around a year. Without control groups, the value of these case series were deemed limited. They do

report before and after improvements, showing that Chondrosphere is clinically effective, and also that Chondrosphere can be implanted arthroscopically.

3.2. Submitted Cost-effectiveness evidence and ERG critique

The submission provided a Markov model which was meant to be based on the recent ACI MTA model [20]. The model had annual cycles, a lifetime horizon and transitions between each health state at the end of each cycle. During the first cycle of the model, all patients receive the first repair. These patients can then move into one of three health states: success, no further repair (NFR) or a second repair, if necessary. Subsequent to the first cycle, those who were a success either remain a success or move to a second repair. All those in NFR remain in NFR. The patients who receive the second repair can move into one of two health states: success or NFR. Those who were in the successful health state either remain a success or move to NFR. All those in NFR remain in NFR. No further repairs are possible after a second repair. The ERG judged the model structure to be appropriate. However, the company model differs from that of the ACI MTA model in one crucial respect: first repair successes cannot lose response and move into the NFR health state. This is likely to bias the analysis in favour of the ACIs including Chondrosphere. 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. From age 55, a common probability of patients receiving knee replacements is applied. The perspective, time horizon and discount rates followed NICE recommendations, and were appropriate to the decision problem.

Four main comparators were modelled in the submission which included.

- A first microfracture repair with the possibility of a second microfracture repair
- A first microfracture repair with the possibility of a second ACI repair
- A first ACI repair with the possibility of a second microfracture repair
- A first ACI repair with the possibility of a second ACI repair

Here ACI could be Chondrosphere, ChondroCelect or MACI. When a second ACI repair is followed by a second ACI repair the same ACI is given. ERG expert opinion suggests that this is reasonable because centres are likely to specialise in a single type of repair. However it is possible that Spherox may have advantages in patellar defects and might be used if another form of ACI failed.

The company derives the clinical effectiveness estimates from its NMA on success rates and failure rates, which informed the transition probabilities for the economic model. The ERG also noted that the response estimates for second repairs are only applied once within the modelling as the company did not compound it over the two years to derive the accurate two year response rate. As a

consequence the method used by the company to derive these is incorrect, as the response rates for second repairs are modelled as being much higher than the response rates for first repairs.

The company accepted that the probabilities of second repair successes losing success and moving to NFR are incorrect. It suggests revising these to be based upon the annualised first repair non-response probabilities at two 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 ERG noted that the company clinical effectiveness estimates are incorrect as the company supplied a revised set of response estimates but did 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 Chondrosphere.

The company quality of life estimates are aligned with those of the ACI MTA. ACI MTA model used quality of life values for first and second repair health states from Gerlier et al[21] who analyse the TIG/ACT trial 5 year follow-up, and for knee replacement health states from three separate sources[21-23]. Gerlier et al mapped to the SF-36 data collected during the TIG/ACT trial to quality of life values using the Brazier et al [24] SF-36 to SF-6D to quality of life mapping function.

The unit costs are also largely aligned with those of the ACI MTA model. Cell costs are £10,000 for Chondrosphere, compared with £5,300 to £18,300 for the technologies in the ACI MTA. However, the company does not apply the preferred set of unit costs of the ACI MTA FAD. The company assumed that Spherex 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. Unit costs of outpatient and rehabilitation visits are taken from NHS reference costs[25]. Unit costs of knee replacements are taken from the 2016-17 National Prices and Tariff. Unit costs are in 2015/16 and 2016/17 prices.

Following clarification questions the company revised some of its clinical effectiveness estimates. The ERG provided a scenario analyses using direct evidence from COWISI data rather than the NMA, no further benefit of MF after five years and the unit costs from the ACI MTA FAD.

The company revised cost effectiveness estimates reported that the cost effectiveness of Chondrosphere relative to MF is £4,360 per quality-adjusted life year (QALY) gained and £5,294 per QALY gained for Chondrosphere followed by Chondrosphere when compared with MF only. The cost effectiveness of MACI compared to Chondrosphere is approximately £18k per QALY.

There are no sensitivity analyses around the revised company estimates. The original modelling was most sensitive to the assumption that all MF repair successes fail at year 5.

3.3. Appraisal by NICE and final guidance

The NICE appraisal committee B met in October 2017. The committee concluded that MF was the most relevant comparator for defects up to 2cm² while for those larger than 2cm², the most relevant one was best supportive care given the issue of availability with ACI in the NHS. The committee agreed on the generalisability of the trial populations presented in the submission to patients within the NHS. It concluded that the most relevant source of evidence is the COWISI RCT. Indeed, the committee agreed it was not appropriate to undertake a NMA given the severe imbalance of baseline characteristics across the included studies pertaining to ACI. Based on the two RCTs presented by the company, the committee concluded that in patients with small lesions Chondrosphere was at least as effective as MF while in those with larger lesions Chondrosphere improves outcomes up to 4 years compared to baseline.

The committee concluded that the ERG's scenario analyses for the cost-effectiveness analyses were the most relevant for decision making. They also noted that there is considerable uncertainty surrounding the incremental cost-effectiveness ratios because the long-term benefit of Chondrosphere is yet to be established. The Committee noted that Chondrosphere was cheaper than the other ACI technologies appraised in the ACI MTA. The committee considered Chondrosphere was likely to be cost-effective for treatment of patients with defect size larger than 2cm².

NICE guidance [26] was issued in March 2018 and was as follows:

“Autologous chondrocyte implantation (ACI) using Chondrosphere is recommended as an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV) in adults, only if:

- the person has not had previous surgery to repair articular cartilage defects
- 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) and the defect is over 2cm²”

4. Acknowledgements:

The views expressed in this report are those of the authors and not necessarily those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. Any errors are the responsibility of the authors.

5. Author Contributions:

XA, EC, AM, PR, RJ, JR, NW and HM were authors of the ERG report on which that this paper is based. XA, MC and HM produced the first draft of the manuscript. All authors commented on the manuscript and approved the final version. This summary has not been externally reviewed by PharmacoEconomics.

6. Compliance with Ethical Standards

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6.2. Conflicts of Interest

XA, EC, MC, AM, PR, RJ, JR, NW and HM have no conflicts of interest that are directly relevant to the content of this article.

7. References

1. International Cartilage Repair Society. *ICRS SCORE/GRADE*. 2000 [25/07/2016]; Available from: <https://cartilage.org/society/publications/icrs-score/>.
2. National Institute for Health and Care Excellence. *Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects [ID851]*. 2017 [14/08/2017]; Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10162>.
3. National Institute for Health and Care Excellence. *Knee cartilage defects - autologous chondrocyte implantation [ID686]: In development [GID-TAG446]*. 2017 [15/08/2017]; Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-tag446>.
4. National Institute for Health and Care Excellence. *Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee: Technology appraisal guidance [TA477]*. 2017 [15/10/2017]; Available from: <https://www.nice.org.uk/guidance/ta477>.
5. Urquhart, D.M., et al., *What is the effect of physical activity on the knee joint? A systematic review*. *Med Sci Sports Exerc*, 2011. **43**(3): p. 432-42.
6. European Medicines Agency. *ChondroCelect*. 2014 [25/07/2016]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000878/human_med_000698.jsp&mid=WC0b01ac058001d124.
7. European Medicines Agency. *MACI: matrix-applied characterised autologous cultured chondrocytes*. 2014 [25/07/2016]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002522/human_med_001660.jsp&mid=WC0b01ac058001d124.
8. European Medicines Agency. *Spherox*. 2017; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002736/human_med_002138.jsp&mid=WC0b01ac058001d124.
9. Becher, C., et al., *Safety of three different product doses in autologous chondrocyte implantation: results of a prospective, randomised, controlled trial*. *J Orthop Surg Res*, 2017. **12**(1): p. 71.
10. Niemeyer, P., et al., *The Effect of Cell Dose on the Early Magnetic Resonance Morphological Outcomes of Autologous Cell Implantation for Articular Cartilage Defects in the Knee: A Randomized Clinical Trial*. *Am J Sports Med*, 2016. **44**(8): p. 2005-14.
11. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials*. *Bmj*, 2011. **343**: p. d5928.
12. Saris, D., et al., *SUMMIT Prospective, Randomized, Controlled Trial: Response Rates To Matrix-induced Autologous Chondrocyte Implant (MACI) Versus Microfracture (MFX) By Lesion Characteristics*. *Orthopaedic Journal of Sports Medicine*, 2013. **1**(4 Suppl): p. 2325967113S00029.
13. Saris, D.B., et al., *Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture*. *Am J Sports Med*, 2009. **37** Suppl 1: p. 10s-19s.
14. Vanlauwe, J., et al., *Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters*. *American Journal of Sports Medicine*, 2011. **39**(12): p. 2566-74.
15. Fickert, S., et al., *One-Year Clinical and Radiological Results of a Prospective, Investigator-Initiated Trial Examining a Novel, Purely Autologous 3-Dimensional Autologous Chondrocyte Transplantation Product in the Knee*. *Cartilage*, 2012. **3**(1): p. 27-42.
16. Maiotti, M., et al., *Transplantation of Tissue-engineered Cartilage for Repair of Osteochondral Defects in the Knee (SS-27)*. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, 2012. **28**(6): p. e15-e16.
17. Roessing, S., et al., *The full arthroscopic technique of autologous chondrocyte transplantation using chondrospheres-safety study with 2 years follow up*. *Cartilage*, 2010. **1** (2 Supplement 1): p. 55S.
18. Schreyer, T., *Comparison in clinical outcome of first generation ACT with ACT of third generation with spheroids*. *Cartilage*, 2010. **1** (2 Supplement 1): p. 58S.

19. Siebold, R., et al., *Second-look assessment after all-arthroscopic autologous chondrocyte implantation with spheroides at the knee joint*. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 2016. **24**(5): p. 1678-1685.
20. Mistry, H., et al., *Autologous chondrocyte implantation in the knee: systematic review and economic evaluation*. Health Technol Assess, 2017. **21**(6): p. 1-294.
21. Gerlier, L., et al., *The Cost Utility of Autologous Chondrocytes Implantation Using ChondroCelect (R) in Symptomatic Knee Cartilage Lesions in Belgium*. Pharmacoeconomics, 2010. **28**(12): p. 1129-1146.
22. Dong, H. and M. Buxton, *Early assessment of the likely cost-effectiveness of a new technology: A Markov model with probabilistic sensitivity analysis of computer-assisted total knee replacement*. Int J Technol Assess Health Care, 2006. **22**(2): p. 191-202.
23. Jansson, K.A. and F. Granath, *Health-related quality of life (EQ-5D) before and after orthopedic surgery*. Acta Orthop, 2011. **82**(1): p. 82-9.
24. Brazier, J., J. Roberts, and M. Deverill, *The estimation of a preference-based measure of health from the SF-36*. J Health Econ, 2002. **21**(2): p. 271-92.
25. Department of Health. *NHS reference costs 2012 to 2013*. 2013 20/09/2017]; Available from: <https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013>.
26. National Institute for Health and Care Excellence. *Autologous chondrocyte implantation using chondrosphere for treating symptomatic articular cartilage defects of the knee*. 2018; Available from: <https://www.nice.org.uk/guidance/ta508/resources/autologous-chondrocyte-implantation-using-chondrosphere-for-treating-symptomatic-articular-cartilage-defects-of-the-knee-pdf-82606726260421>.

Table 1: Compared baseline characteristics of studies included in the network meta-analysis

Variable	COWISI		SUMMIT [12]		TIG/ACT [13, 14]	
Study sponsor	Co-Don		Sanofi (Vericel)		TiGenix	
Region/Country	EU: Germany and Poland		EU: Czech Republic, France, Netherlands, Norway, Poland,		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 \pm SD	36 \pm 10	37 \pm 9	34.8 \pm 9.2	32.9 \pm 8.8	33.9 \pm 8.5	33.9 \pm 8.6
Male sex (%)	33 (63.5)	28 (56.0)	45 (62.5)	48 (66.7)	35 (61)	41 (67)
BMI (kg/cm ²) \pm SD	25.7 \pm 3.3	25.8 \pm 3.0	26.2 \pm 4.3	26.4 \pm 4.0	28 (49%) and 26 (46%) with a BMI \leq 25 and >25 to \leq 30 respectively	31 (51%) and 24 (39%) with a BMI \leq 25 and >25 to \leq 30 respectively
Lesion size cm ²	2.2 \pm 0.7	2.0 \pm 0.8	4.9 \pm 2.8	4.7 \pm 1.8	2.6 \pm 1.0	2.4 \pm 1.2
Previous repair procedures affecting subchondral bone n (%)	■		marrow stimulation techniques (34.6%),		14% (MF 5, drilling 3, abrasion 1)	7% (MF 1, drilling 2, abrasion 1)
Duration of symptoms (years)	■	■	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		single grade III to IV symptomatic cartilage defects of the femoral condyles	

			femoral condyle (LFC) and/ trochlea			
Outerbridge grade n (%)						
III	■	■	21 (29.2)	15 (20.8)	10 (18)	16 (26)
IV	■	■	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	■	18 (25.0)	9 (12.5)	NA	NA
Osteochondritis dissecans	none	■	8 (11.1)	12 (16.7)	NA	NA
Unknown	none	■	9 (12.5)	6 (8.3)	NA	NA
Other	32	■	4 (5.6)	0	NA	NA
Baseline KOOS score						
Overall	■	■	NA	NA	56.3 ± 13.6	59.5 ± 14.9
Pain	■	■	37.0±13.5	35.5±12.1	62.1 ±18.73	65.5 ±17.1
Function	■	■	14.9 ± 14.7	12.6 ± 16.7	NA	NA
Concomitant surgery	0	0	36%	31%	7%	11%

EU: European Union; MF: microfracture; MACI: autologous cultured chondrocytes on porcine collagen membrane; SD: standard deviation; BMI: body mass index; ICRS: International Cartilage Repair Society; KOOS: Knee Injury and Osteoarthritis Outcome Score

The redacted sections correspond to information provided by the company in confidence for the purpose of the appraisal