Document prepared for the NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

Matrix applied characterised autologous cultured chondrocytes implantation - (MACI®)

Submission of Aastrom Biosciences

August 2014

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Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Maxtrix applied characterised autologous cultured chondrocytes implantation (brandname: MACI® (MACI)) an Advanced Therapy Medicinal Product (ATMP) defined as a combined tissue-engineering product (TEP) allows for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III to IV on the modified Outerbridge Scale) with a defect size of 3-20 cm2, as a result of sports injury or trauma, in skeletally mature individuals with a lesion that can be due to mild degenerative changes but not severe degeneration. A positive opinion of the CHMP was received on 26th April 2013 via the centralised procedure. A Marketing Authorisation for the EU was received on 27th June 2013.

MACI implant is a cartilage repair procedure in which a patient's own chondrocytes are used to grow new cartilage in the site of an existing cartilage defect. Each implant contains matrix applied characterized autologous cultured chondrocytes. Each MACI implantation matrix contains 500,000 to 1,000,000 cells/cm2 on a 14.5 cm2 type I/III collagen membrane, to be trimmed by the surgeon to the size and shape of the defect. Using the MACI implant procedure, chondrocytes are removed from less-weight-bearing areas of the knee during arthroscopy and are expanded and cultured under supervision in a laboratory under GMP conditions. The cultured chondrocytes are then be uniformly seeded using the proprietary Uniform Loading Unit (ULU) onto a collagen scaffold or 'matrix' in the laboratory, which is then implanted, cell-side down, to fill the cartilage defect during a second surgery. Patients receive only one implant. MACI is technically easier to implant and quicker than conventional ACI.

The main comparator for MACI is microfacture (MF) as this is a proven and suitable alternative for all lesion sizes. MF involves the creation of perforations 3 to 4 mm apart in the subchondral bone to release bone marrow elements,

which include stem cells and growth factors, into the lesion, to induce cartilage repair. It has been frequently performed in patients since 1984. Due to its frequent use, MF has been used as the comparator treatments in most comparative studies of newer treatments. Usually MF is not performed in lesions large than 12-13 cm2.

Mosaicplasty, which involves the removal of cylindrical osteochondral plugs (cartilage and bone) from less weight-bearing parts of the knee followed by transplantation into the damaged area, can also be seen as a possible comparator though there is less evidence for this treatment in the published literature. Mosaicplasty is most appropriate for lesions between 2 and 4 cm2.

The key evidence for this submission is provided by the SUMMIT trial and its 3-year extension study for which 1-year results are now available and included in this submission. In addition a small RCT by Basad was also identified.

The SUMMIT trial is a prospective, randomised, open-label, parallel-group, multi-centre study, sponsored by Genzyme (Sanofi). The study compared MACI implant (N=72) with MF (N=72) in patients aged 18 to 55 with Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm^2. The co-primary outcomes in the trial were change from baseline to Week 104 in knee injury and osteoarthritis outcome score (KOOS) pain score and KOOS function (sports and recreational activities (SRA) score. The study was followed by a three-year extension study. Results from both studies have been included in this clinical section of the MACI submission.

The co-primary efficacy outcome for SUMMIT was change in KOOS Pain and Function (SRA) scores from baseline to Week 104. The KOOS is a validated instrument with a normalized score that is calculated with 100 indicating no symptoms and 0 indicating extreme symptoms. Treatment with MACI implant resulted in a significantly greater increase in KOOS Pain and Function scores from the baseline level compared with microfracture (p=0.001). The difference in mean change in pain score was 11.76 and the mean change in function (SRA) score was 11.41. Similar results were also found for the PP analysis.

In a subgroup of patients with chondral defects sized <4 cm^2, treatment with MACI implant resulted in a greater increase in KOOS Pain and Function score from the baseline level compared with microfracture. The difference in mean change in Pain score was 12.59 and the mean change in Function (SRA) score was 10.16.

Therefore, for the ITT and PP analyses and subpopulation of patients with defect size <4 cm^2, for the primary efficacy outcome, MACI implant is superior to microfracture. MACI implant was also statistically superior to microfracture for response rate based on KOOS scores and change in other KOOS domain scores

In terms of safety, in the SUMMIT study, the most frequently reported adverse events (AEs) for patients treated with MACI was arthralgia which was lower than that of the comparator. Overall, the frequency of other reported common AEs, severe AEs and SAEs was low.

The SF-12 was used to measure health-related quality of life in the SUMMIT trial. A summary of the change in SF-12 Physical and Mental Component Scores, transformed into z-scores, is presented in Table 18 . From Baseline to Week 104, patients in both treatment groups had substantial increases in their Physical and Mental Component Scores. There was no significant difference between treatment groups in the improvement in the Mental Component Score (p=0.523). In contrast, patients who were treated with MACI implant experienced significantly greater improvements in their Physical Component Score compared with patients treated with microfracture (p=0.001). This result underlines the superior improvements in physical well-being achieved by treatment with MACI implant.

For the SUMMIT extension study

[redacted]

Secondary efficacy outcomes

The Basad study_compared the clinical outcomes of patients in a German clinic with symptomatic cartilage defects treated with MACI (N=40) or microfracture (N=20). The study was a 2-year, randomised trial, which included patients ≥18 and ≤50 years of age with symptomatic, post-traumatic,

single, isolated chondral defects (4–10 cm^2). The primary outcome measures were the Tegner, Lysholm and ICRS scores. Five-year data are likely to be published within the next 12 months however we do not have access to these data at this point. Results showed that the difference between baseline and 24 months post-operatively for both treatment groups was significant for the Lysholm, Tegner, patient ICRS and surgeon ICRS scores ($P<0.0001$). However, MACI was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm ($P = 0.005$), Tegner ($P = 0.04$), ICRS patient ($P = 0.03$) and ICRS surgeon ($P = 0.02$) scores. There were no safety issues related to MACI or MF during the study. Therefore MACI was considered superior to MF in the treatment of articular defects over 2 years.

The clinical data presented in this submission relate to those studies identified from a prior systematic literature review conducted for an MSAC submission for MACI in Australia in January 2013. This review was supplemented with data that were published since, which were identified by Aastrom using a focused approach. Though initially planned, due to time constraints related to the recent purchase of MACI by Aastrom it was not possible to fully update the systematic literature review, nor was it possible to update the indirect comparison which was also carried out for the MSAC submission. This involved an indirect comparison of the SUMMIT trial 2- year data only as the 1-yr extension data were not yet available.

Furthermore, it was also not possible to carry out a cost-effectiveness analysis. Cost-effectiveness evidence was presented in the MSAC submission in January 2013 and it was the aim to adapt this model to the English and Welsh situation, however due to time constraints in terms of the submission timelines and the purchase by Aastrom, this was not possible. Therefore, there is no economic evidence available for MACI for England and Wales.

The Australian cost-effectiveness model, which was based on the SUMMIT trial concluded that MACI was cost-effective. The submission in Australia focussed on lesion sizes between 2-4 cm2. However, MACI was not listed in Australia due to a purported lack of evidence on the short-term and long-term benefits of (M)ACI versus MF and mosaicplasty though the MSAC did agree

in their report " that MACI and/or ACI may potentially be more effective for patients with large chondral lesions (>2cm2), however this was not supported by high quality evidence". However this evidence is now available. In addition the target group is lesion sizes between 3 and 20 cm2.

In terms of budgetary impact, it is expected that a maximum of ~10,000 patients in the UK will have a cartilage lesion requiring repair. It is expected that ~500 of these will qualify for treatment with MACI or similar technologies. Given that there are likely to be two similar treatments available involving autologous chondrocyte implantation, we assumed that the market would be split equally between these two treatment options and that they would each reach 250 units at year 5. This is accompanied by a budgetary impact of £8.3m in year 5 if the failure rates for MACI (and ACI) and MF are used from the SUMMIT trial and allowing MACI to be used in first-line (as well as ACI which has a higher acquisition cost but similar efficacy) versus the current situation where it was assumed that MACI and ACI would be used after prior failure of MF. If however, failure data are used from the Saris 2009 publication the budgetary impact is reduced to £7.8m in year five, indicating that part of the acquisition cost of MACI is offset by the superior performed of MACI versus MF.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Maxtrix applied characterised autologous cultured chondrocytes implantation (brandname: MACI® (MACI)) an Advanced Therapy Medicinal Product (ATMP) defined as a combined tissue-engineering product (TEP) allows for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III to IV on the modified Outerbridge Scale) with a defect size of 3-20 cm2, as a result of sports injury or trauma, in skeletally mature individuals with a lesion that can be due to mild degenerative changes but not severe degeneration.

1.2 What is the principal mechanism of action of the technology?

MACI implant is a cartilage repair procedure in which a patient's own chondrocytes are used to grow new cartilage in the site of an existing cartilage defect. Each implant contains matrix applied characterized autologous cultured chondrocytes. Each MACI implantation matrix contains 500,000 to 1,000,000 cells/cm2 on a 14.5 cm2 type I/III collagen membrane, to be trimmed by the surgeon to the size and shape of the defect. Using the MACI implant procedure, chondrocytes are removed from less-weight-bearing areas of the knee during arthroscopy and are expanded and cultured under supervision in a laboratory under GMP conditions. The cultured chondrocytes

are then be uniformly seeded using the proprietary Uniform Loading Unit (ULU) onto a collagen scaffold or 'matrix' in the laboratory, which is then implanted, cell-side down, to fill the cartilage defect during a second surgery. (1;2)

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. A positive opinion of the CHMP was received on 26th April 2013 via the centralised procedure. A Marketing Authorisation for the EU was received on 27th June 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The EPAR document was based on the 2- year data from the SUMMIT trial; a prospective, randomised, open-label, parallel group multi-centre study comparing MACI (N=72) with microfracture (MF) (N=72) in patients aged 18 to 55 with Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm^2. The co-primary outcomes in the trial were change from baseline to Week 104 in knee injury and osteoarthritis outcome score (KOOS) pain score and KOOS function (sports and recreational activities (SRA) score. For MACI to show superiority over MFX; a statistically significant difference had to be seen in both KOOS Pain and Function (sports and recreation) individually not collectively.

The main issues discussed in the EPAR were the fact that the benefit of MACI is not restricted to a particular lesion size and that lesion size does not affect treatment effect. The efficacy demonstrated in the clinical studies is supported by data from the literature. The studies consistently show a relevant

improvement of pain and function of the knee that is persistent over the years. In terms of safety, in the SUMMIT study, the most frequently reported adverse events (AEs) for patients treated with MACI was arthralgia which was lower than that of the comparator. Overall, the frequency of other reported common AEs, severe AEs and SAEs was low. Overall, the results of the SUMMIT study based on 2-yr data, showed a favourable safety profile for MACI relative to microfracture, this despite MACI requiring two surgeries, compared one for MF.

The EPAR mentioned the following important risks related to MACI: symptomatic graft hypertrophy or graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft failure); or peri-operative complications related to surgical intervention of the knee: haemarthrosis, arthrofibrosis, localised surgical site inflammation, localised surgical site infection or thromboembolic events. It further noted that, many of the risks observed with MACI are mostly related to the quality and accuracy of the surgical techniques used in administering MACI and to the quality of the rehabilitation of the patients. Therefore it is important that patients should follow an appropriately controlled, phased rehabilitation programme based on the MACI rehabilitation manual.(2)

The EPAR further made mention of the pediatric use of MACI, ie in individuals younger than 18 years of age. A pediatric investigation plan (PIP) was agreed with then Sanofi prior to receipt of the Marketing Authorisation. In this PIPpatients younger than 18 years of age but who were treated with MACI (this means that these individuals had closed growth plates), will be followed up for a period of five years for safety.

Another point that was discussed in the EPAR included the fact that age is not a predictor of efficacy for MACI, nor is lesion size, ergo MACI can be used in all patients aged between 18 and 55.

A final aspect that we mentioned was the fact that EMA requested additional information on the activity of the implanted chondrocytes. A newly developed assay was used to ensure the quality of the batches manufactured, however Sanofi/Aastrom have agreed to develop a new potency assay validated

against the ability to form stable cartilage as detailed in the risk management plan with a due date of December 2016. This was also requested of other ACI products (ie. ChondroCelect®).

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The indication of MACI is the repair of symptomatic, full-thickness cartilage defects of the knee (grade III to IV on the Modified Outerbridge Scale) with a defect size of 3-20 cm^2 in skeletally mature adults.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are no additional studies planned at this moment or on-going at Aastrom. However, Dr Basad's RCT comparing MACI to MFX for which two-year data has been published, 5-year follow-up data are likely to be published during the next 12 months.(3) It is likely that 1yr data from the SUMMIT Extension Study (3yr follow up of the SUMMIT cohort) will be presented at congresses in 2015 so an abstract may be available before guidance is published.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

MACI was originally launched in the UK in 2000 and was used in both England and Wales but was subsequently withdrawn from the market in 31 Dec 2012 because of a change in the licensing legislation requiring the product to go through a full regulatory approval using the centralised procedure. Similar products (ChondroCelect®) were obliged to undergo the same process. The centralised procedure was started in September 2011 to obtain a full marketing authorisation. The Named Patient programme covered

the period from 31st Dec 2013 until 27th June 2014 only. Prior to 31st Dec 2013 MACI was commercially and freely available. Between September 2011 and 31st December 2012 approximately 60 patients were treated. Following EMA approval, the name-patient scheme ceased. No MACI were implanted in second half of 2013 as physicians needed to be retrained and accredited Using the MHRA approved online training programme which took about six months. Since January 2014 MACI's first commercial under the ATMP classification was 28th May 2014. The use of MACI is expected to cease 26th August 2014 as a consequence of the sale of MACI by Sanofi to Aastrom. Aastrom have elected to close the Danish site where MACI is currently being produced and to move production to their site in the US. The last patient treated with MACI before the temporary suspension is expected to be 20th August 2014. It is expected that MACI will be once more available in England and Wales in about 12 months' time, when the US production site is expected to be fully operations.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes MACI has a centralised Europe license from EMA.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

There is no other HT assessment on-going at this point in time in the UK.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1 Unit costs of technology being appraised

Pharmaceutical formulation	Matrix for implantation
Acquisition cost (excluding VAT)	£16,226
Method of administration	Surgery
Doses	1 per patient
Dosing frequency	1 per cartilage defect
Average length of a course of treatment	From biopsy to implant: approx. 97% of patients are implanted 6 weeks after the biopsy
Average cost of a course of treatment	£16,226 + theatre time for biopsy + theatre time for surgery + rehab
Anticipated average interval between courses of treatments	NA
Anticipated number of repeat courses of treatments	None
Dose adjustments	None

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not Applicable as MACI is not a device.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional costs required, just the standard assessment used by surgeons to determine the presence of a cartilage lesion. These entail the following: It is expected that prior to the decision to use MACI, or any cartilage repair/regeneration technique, the treating physician would carry out tests on the affected knee, most likely some form of radiological investigation (probably MRI) to confirm that the patient indeed has a cartilage lesion. Furthermore, most surgeons will also carry out an arthroscopic confirmation of the damage. At this confirmation arthroscopy, if the possibility of using MACI had been discussed with the patient, the physicians would also harvest the required

cartilage cells using a biopsy at that time, thus removing the need for an additional biopsy.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There are no other therapies that are likely to be administered as part of the course of treatment with the exception of regular analgesics and appropriate surgical antibiotic prophylaxis as per local hospital policy.

Other reconstructive surgery may also be performed, if deemed necessary by the surgeon, to correct any malalignment, meniscal or ACL damage.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Articular (hyaline) cartilage in the knee distributes the load between the femur and tibia to avoid high point stresses on load-bearing areas within the knee and to provide a low friction-bearing surface, assisted by the synovial fluid. After an individual reaches skeletal maturity, their articular cartilage does not spontaneously heal or regenerate. Furthermore, hyaline cartilage, constructed from type II collagen, does not have a blood, nerve, or lymphatic supply which could induce or help mediate an intrinsic repair response.

Damage can occur due to sports injuries, other trauma, progressive mechanical degeneration or osteochondritis dissecans, a joint disorder of unknown aetiology, in which cracks form into the articular cartilage. Once damaged, cartilage does not heal and therefore injuries involving damage to cartilage need to be treated.

Cartilage defects of the knee occur along a spectrum of size and severity, ranging from small, acute non-symptomatic lesions that are often diagnosed incidentally at the time of knee arthroscopy, to larger, more chronic often symptomatic lesions that cause a reduction in mobility and pain during movement. If left untreated, this can be start of the process of degeneration of the cartilage and knee joint, which leads to deformities, osteoarthritis, continuous pain, catching, locking, and swelling. and the possible need for total knee replacement.(2;4)

Cartilage defects are very disruptive to the individual. The Heir study shows that cartilage lesions cause the same degree of disability, pain and loss of function in this otherwise healthy population as severe osteoarthritis (OA) does in older patients waiting for total knee replacement (TKR). Heir also

points out that TKR would be inappropriate in this younger age group. This emphasises why effective cartilage repair should be undertaken for the health/societal gain for this young population.(5)

Cartilage defects of the knee are mostly diagnosed via MRI or often coincidentally during an arthroscopy in case of meniscal damage. In case a preliminary diagnosis has been made via MRI, an arthroscopy will be necessary to understand the nature of the lesion. The lesion size is usually only confirmed after debridement. To classify the lesions the Outerbridge Scale is often used, a grading system for joint cartilage breakdown.(6)

- Grade 0 - normal
- Grade I - cartilage with softening and swelling
- Grade II - a partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
- Grade III - fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm
- Grade IV - exposed subchondral bone

Grades III and IV represent full-thickness cartilage defects of the knee that are lesions considered for possible treatment with MACI.

The exact incidence of symptomatic chondral knee lesions in the overall population is unknown. In some large-scale epidemiological studies, cartilage injuries were observed in 5-11% of diagnostic knee arthroscopies in predominantly young adult populations with knee pain.(2)

The past two decades have seen the development of several treatment modalities for cartilage repair.(7) There are currently three main surgical treatments available for cartilage defects. 1) microfracture (MF) which involves the creation of perforations 3 to 4 mm apart in the subchondral bone to release bone marrow elements, which include stem cells and growth factors, into the lesion, to induce cartilage repair. It has been frequently performed in patients since 1994. 2) mosaicplasty, which involves the removal of cylindrical osteochondral plugs (cartilage and bone) from less weight-bearing parts of the

knee followed by transplantation into the damaged area and 3) the transplantation of autologous chondrocytes (the cells found in cartilage). The chondrocytes are harvested arthroscopically, consequently cultured in vitro and then re-implanted in the knee to regenerate hyaline cartilage at the lesion site This technique was first reported in 1994 and has been increasingly used over time. An evidence review of the published literature of demonstrated that matrix-induced autologous chondrocyte implantation is a promising third-generation cell therapy for the repair of symptomatic, full-thickness articular cartilage defects.(8)

There are no internationally accepted treatment guidelines on how and when to treat cartilage lesions. A recent survey involving 242 European orthopaedic surgeons revealed a consensus for debridement and/or MF as a first-choice treatment for full-thickness cartilage lesions up to 3 cm^2, but for the treatment of lesions >3 cm^2 there was less agreement; where (M)ACI was preferred by 33.5% of the experts, followed by MF (19.0%), debridement (15%) and with lesser frequency osteochondral plug transplantation (9.5%), and several other techniques. Furthermore there are no UK guidelines available although these are in development.(2). Most lesions requiring treatment have a size between 3-20 cm^2.(9)

To measure the extent of the damage as well as the effect the treatment of knee injuries a variety of outcome measures can be used. Clinical measures include MRI and histology assessment. Patient-reported outcome measures include the Knee Injury and Osteoarthritis Outcome Score (KOOS), a validated global knee score suitable for comparison of patients with knee complaints attributable to different causes, the SF-36 (a generic quality of life questionnaire), the 6-minute walk test, active knee range of motion (ROM), and pain visual analog scales.(5) The KOOS is a validated instrument and is generally considered as the main PRO in cartilage repair and is included in most clinical trials. The KOOS consists of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life (QOL). The previous week is the time period considered when answering the questions. Standardized answer options are

given using a Likert scale ranging from 0 to 4. A normalized score is calculated with 100 indicating no symptoms and 0 indicating extreme symptoms. Special scoring instructions are available for subscale. KOOS is completed by patients, is easy and quick (10 minutes) to complete.(10-17)

Whilst there are international rehabilitation guidelines as issued by the International Cartilage Repair Society (ICRS) that apply to rehabilitation after articular cartilage damage, providing guidance related to duration and exercise regimes. Rehabilitation is a personalized process but general required between 3 to 6 months post-intervention to return to functional activity (without running and jumping.(18) The rehabilitation programme developed following extensive research by Ebert and colleagues specifically for the MACI implant, is designed to maximize both the healing process and maturation of the MACI implant and to return the patient to as near normal function as possible.

After repair, most improvement occurs in the first year; however, maximum improvement is often not seen until two to three years post-operatively. (Full) Recovery is long because of the physiologic remodeling. Furthermore, the speed of this process varies among patients.

Not all patients will be treated successfully. An 11-yr follow-up study involving 75 patients treated with MF to repair cartilage damage to the knee (1981-1991) showed that about 20% of patients who had persistent pain at 3, 5, and 7 years did not elect to undergo further surgery suggesting that many of the unimproved patients chose to live with their disability as opposed to undergoing more extensive procedures.(19)

Furthermore, a systematic review of the literature that identified 15 studies that involving MF (six long-term and nine short-term studies), comparing clinical outcomes of MF with those of other treatments showed that overall, small-sized lesions and younger patients showed good results in the short-term. However, osteoarthritis and treatment failures were observed later, between 5 to 10 years post-operatively leading the authors to conclude that

beyond 5 years post-operatively, treatment failure after MF could be expected regardless of lesion size.(7)

There are few studies reporting outcomes of treatment by age, though there is some data available indicating that clinical results after MF (for full-thickness cartilage lesions in the knee) are age-dependent with better results in patients aged 40 and younger.(7;20)

A study reporting long term (9.8 years) results post intervention, comparing MF versus mosaicplasty conclude that there were no significant differences between either group in patient-reported outcomes, muscle strength or radiological outcome.(21)

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

It is expected that a maximum of ~10,000 patients in the UK will have a cartilage lesion requiring repair.(22) It is expected that ~500 of these will qualify for treatment with MACI or similar technologies.(23)

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

The current affliction and treatment do not, in the vast majority of cases, increase mortality and therefore it is expected that individuals with cartilage defects of the knee and treated with MACI will have a life expectancy in line with those of the general population of the same age and gender.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE reviewed autologous chondrocyte implants in the technology appraisals [TA89] with a publication date of May 2005, which concluded that "ACI is not recommended for treating knee problems caused by damaged articular cartilage, unless it is used in studies that are designed to produce good-quality information about the results of the procedure. These results should include measuring any improvement in patients' quality of life, and the benefits and risks of ACI over a long period of time." And continued to say that " If ACI is offered as part of a clinical study, the doctor should explain that there are uncertainties about the long-term benefits of this procedure and the possible risks, such as locking of the knee, infections and not being able to fully straighten the leg". This decision was based on the fact NICE was not persuaded that the data (including new data made available at the time which at times was deemed inconsistent) were sufficient to establish the effectiveness of the technology. NICE further noted that the cost-effectiveness evidence involved too much uncertainty so that it was not possible to establish the ICER with any real certainty, again mainly due to the lack of good effectiveness data, especially data establishing long(er)-term effectiveness. Furthermore, health-related quality of life data on patients who undergo ACI and other procedures, including knee replacement, were also considered inadequate. In light of the above, NICE agreed that it would be important to obtain evidence on whether ACI reduces the need for long-term joint replacement and to assess long-term adverse effects. Better information on patient characteristics (such as lesion size) and treatment protocols were also mentioned in the assessment report.(24) It further concluded that ACIs could be used but only as part of a trial to gather additional information on this technology. A related technology, ChondroCelect®, which is a form of autologous chondrocyte implantation, only entered the market in 2008/2009.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There are no internationally accepted treatment guidelines on how and when to treat cartilage lesions. A recent survey involving 242 European orthopaedic surgeons revealed a consensus for debridement and/or MF as a first-choice treatment for full-thickness cartilage lesions up to 3 cm^2, but for the treatment of lesions >3 cm^2 there was less agreement; where (M)ACI was preferred by 33.5% of the experts, followed by MF (19.0%), debridement (15%) and with lesser frequency osteochondral plug transplantation (9.5%), and several other techniques. Furthermore there are no UK guidelines available although these are in development.(2) The launch of MACI in England and Wales would mean that more patients with defects large or equal to 3cm^2 could be treated with MACI.

In terms of the treatment pathway for patients, the introduction of MACI will not affect any meaningful change as surgeons will continue to determine the most appropriate course of action for cartilage lesions of the knee as before.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Currently there is no validated consensus statement in the UK, each centre will have their own best clinical practice. There is a consensus paper due out signed and approved by more than 30 UK knee surgeons and backed by the British Association of Surgery of the Knee (BASK).

2.7 Please identify the main comparator(s) and justify their selection.

The main comparator for MACI is microfracture (MF) as this is a proven and suitable alternative for all lesion sizes. MF involves the creation of perforations 3 to 4 mm apart in the subchondral bone to release bone marrow elements, which include stem cells and growth factors, into the lesion, to induce cartilage repair. It has been frequently performed in patients since 19984. Due to its frequent use, MF has been used as the comparator treatments in most comparative studies of newer treatments.(7;19-21;25-29) Usually MF is not performed in lesions large than 12-13 cm^2(19).

Mosaicplasty, which involves the removal of cylindrical osteochondral plugs (cartilage and bone) from less weight-bearing parts of the knee followed by transplantation into the damaged area, can also be seen as a possible comparator though there is less evidence for this treatment in the published literature. Mosaicplasty is most appropriate for lesions between 2 and 4 cm^2.(21;30;31)

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Any adverse events that would occur would be mostly associated with the surgery rather than MACI perse. This is clear from the TEAE which show mostly surgery related AEs such as joint effusion and joint pain. Therefore the adverse events that can be expected are arthralgia and pain and possibly surgical site infections, which could occur with any related treatment also.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

MACI implantations are generally carried out in centres of excellence. In terms of resource use, the main resource use would be for operating theatres, using as a day-case for biopsy and an overnight stay for the implantation of MACI. The actual duration of the implantation is 1.5hrs using a full theatre. Administration costs will involve those related to the routine booking of operations and the review of patients and any other extras would be as per the license obtained from EMA. No specific monitoring or tests outside of those provides as part of routine good medical care.

2.10 Does the technology require additional infrastructure to be put in place?

The technology does not require an additional infrastructure to be put in place but can be managed within the current NHS framework. Given that surgical skill is important for treatment success, the use of MACI is most likely to be

limited to experienced treatment specialised treatment centres in England and Wales such as RNOH Stanmore and RJAH Oswestry.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 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

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There is no evidence to suggest that the use of MACI is associated with any equality issues

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

MACI is a third generation ACI and represents a marked improvement over the first two generations of autologous chondrocyte implantations:

- ACI-P: This first-generation periosteum-covered ACI was developed because current techniques, at the time, could not treat the entire spectrum of lesions observed, particularly larger defects. Usage was limited due to the technical challenges of the surgery, the invasiveness of the procedure, cost, and postoperative complications such as hypertrophy associated with the periosteal patch.(8)
- ACI-C: second-generation collagen-covered ACI was deemed an improvement on the first generation ACI due to the use of a biodegradable collagen membrane cover instead of an autologous periosteal cover. Reports of this second-generation cell therapy showed clinical improvement similar to that of ACI with fewer complications such as hypertrophy. However, an open surgical technique with sutures was still required.(8)
- MACI (Matrix applied characterised autologous chondrocyte implantation): A third generation ACI whereby the autologous chondrocytes are attached directly only a three-dimensional biodegradable collage type I/III biomatrix or scaffold (manufactured from porcine peritoneal tissue), that is cut to the size and shape of the lesion by the surgeon and is fixed with the use of fibrin glue.

Furthermore, based on the 2-yr SUMMIT study in which SF-12 data were collected, patients treated with MACI experienced statistically significantly greater improvements in their Physical Component Score compared with patients treated with MF (difference in mean change =0.51, p=0.001) demonstrating that the clinical benefits of MACI are translated into relevant HRQoL benefits. (32-34)

EQ-5D data collected alongside the SUMMIT trial, showed that the mean utility score for patients at baseline was 0.481. Patients who responded (10-point increase on the KOOS Pain and Function scores from baseline) to treatment had a mean utility score of 0.833 compared with 0.514 for patients who did not respond to treatment. As MACI was numerically superior to MF at

156 Weeks in terms of treatment response, MACI also causes more patients to have a utility than MF.(32;34)

Compared to other ACI (such as Oscel and ChondroCelect®) MACI is easier to use, as it can be easily cut to size and shape by the surgeon. In addition, evidence provided by Barlett has shown that MACI implantations are quicker to implant meaning requiring less theatre time than other similar implants.(35)

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Yes it could be expected that returning otherwise healthy individuals to full normal activity would have additional health and especially social benefits. This would only be demonstrated with good registry data. To this end, a knee cartilage registry is being set up by the ICRS led by Dr Biant. Other published data comparing patients with osteoarthritis and those with cartilage lesions using the KOOS to measure the extent to which quality of life is impaired within the working population, showed that patients with cartilage lesions have impairments that equal to older patients with osteoarthritis who are expecting to undergo total knee replacement. Furthermore, patients with cartilage lesions had reduced scores on all of the five KOOS subscales, again similar to those seen in patients with osteoarthritis, indicating the extent of the impairment on QoL of cartilage lesions in the knee in relatively young individuals and the potential gain from returning knee functionality in this younger population.(5)

Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.(5)

Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	adults with a symptomatic cartilage defect (chondral defect) but without advanced osteoarthritis”. The chondral defects can be on the femur, tibia or patella.		
Intervention	MACI/ ChondroCelect/ Other ACI	MACI	Aastrom do not have evidence on ChondroCelect
Comparator(s)	Microfacture and Mosaicplasty, (total knee replacement for larger lesions only)	Microfacture and Mosaicplasty	Microfacture and Mosaicplasty
Outcomes	Pain; knee function including long-term function; rates of retreatment; activity levels, such as return to work or sport; avoidance of osteoarthritis, and knee replacement; adverse effects of treatment; health-related quality of life	XX	XX
Economic analysis	Desired	Not available	Not available due to lack of time and funds
Subgroups to be considered	By duration of symptoms (<3 yrs and >3 yrs); Size of lesion; Previous surgery such as microfracture; Cartilage defects secondary to mal-alignment; Non-traumatic causes (eg osteochondritis dissecans); Patients with early OA; Groups by aetiology (sports or occupational injury)	NA	No evidence available on some of these outcome measures
Special considerations, including issues related to equity or equality	None	None	None

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

Due to the very recent purchase of Aastrom from Sanofi, there has not been time to carry out a systematic review of the literature, though this was originally planned by Sanofi. However, a systematic literature review was carried out by Sanofi in 2012 for the submission of MACI to the Australian health technology assessment agency PBAC in January 2013. In addition, Aastrom/Sanofi have always kept a close eye on published literature in this disease area, which is quite contained. Consequently we are confident that all relevant data related to MACI have been identified.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

A full review of the literature was undertaken in Australia in 2013 in order to identify all randomised trials or systematic reviews evaluating the safety and efficacy of MACI implant treatment for patients with chondral defects of the

knee. The search was not limited by comparator, and so could potentially identify any randomised trials or systematic reviews of MACI compared with either microfracture or conservative management. The results of this search were also used to identify MACI observational studies with durations longer than two years.

To ensure that all relevant studies were identified, a comprehensive search of the published literature was conducted. A number of approaches were used to search for relevant data.

- a search of published literature using the electronic database EMBASE.com, which allows concurrent searching of EMBASE and MEDLINE
- a search of the Cochrane Library and other health technology assessment websites
- a search of registers of randomised trials (the clinical trials registries of the National Institutes of Health and the European Union, and the Australian and New Zealand Clinical Trials Registry)
- a search of the Sponsor's database for published and unpublished trial reports

The search strategies used are summarised in Section 10.2 Appendix 2.

All the citations identified in the search were reviewed for eligibility based on an examination of the title/abstract, and if included, the full text. Studies eligible for inclusion were selected by applying the exclusion criteria in Table 2 .

Table 2 Eligibility criteria used in search strategy

	Clinical effectiveness
Exclusion criteria	• not a randomised trial or systematic review • randomised trial does not contain MACI • characteristics of the recruited subjects do not overlap with the main indication • not fully published study

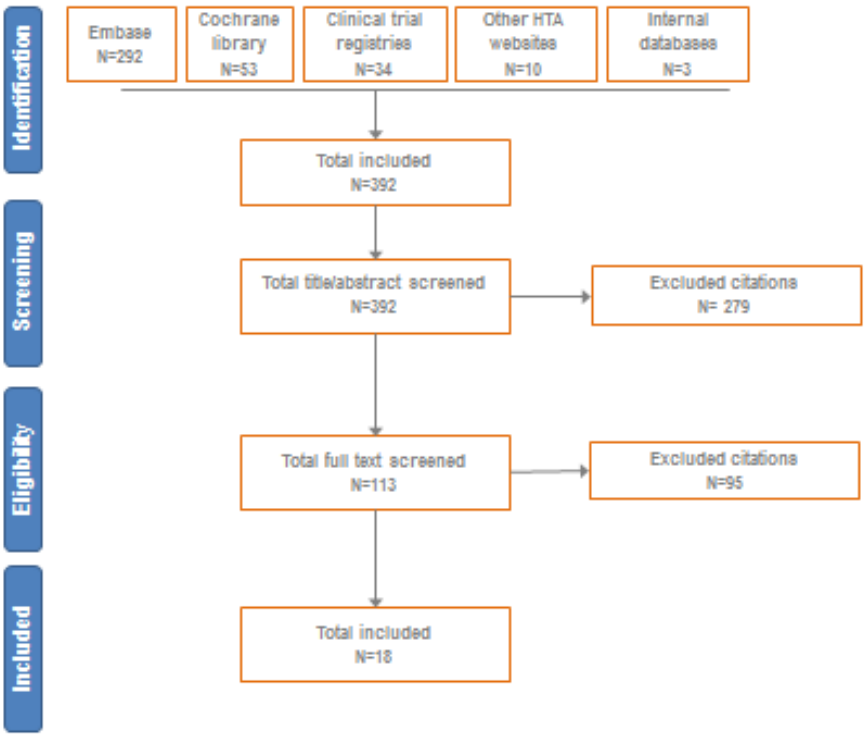
5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

During the MSAC search, a total of 392 unique citations were retrieved, including 292 citations from EMBASE.com, 53 citations from the Cochrane library, 34 citations from clinical trial registries, 10 citations from HTA databases and 3 studies from the Sponsor's internal database. From this search, 18 citations were included; 2 direct randomized trials comparing MACI to microfracture in patients with defect size 2-4 cm^2, 3 other randomized trials including MACI, 8 systematic reviews and 5 long-term studies.

Since the Australian MSAC submission, information from the first year of the open-label, multi-centre, 3-year extension to the SUMMIT study has become available and this has also been included in the evidence base, but is not shown in Figure 1. In addition, evidence from the Basad (2010)(36) study was not included in an Australian MSAC submission but has been included in the evidence base here.

None of the systematic reviews included any MACI implant studies other than those already identified in the literature search and consequently, the analyses from the systematic reviews will not be presented in the current submission.

Figure 1. Flow diagram of included studies from the MSAC systematic review (excluding Basad and SUMMIT extension)



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The SUMMIT(37) trial is a RCT with 2 year follow-up measuring efficacy and safety, which also has an additional ongoing 3 year open-label(38) follow up study, which will yield 5 year medium term data. To date, only the first year data from the 3-year extension study are available.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 3. List of included RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study reference
MACI00206 (SUMMIT) (37)	MACI	Microfracture	Patients with a chondral defect ≥3 cm^2	Saris D, Price A, Widuchowski W *et al.* (2014) Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. Am J Sports Med 42(6):1384-1394
MACI00809 (SUMMIT extension study)(38)	MACI	Microfracture	Patients with a chondral defect ≥3 cm^2	An extension protocol for participants of Genzyme-sponsored prospective, randomized, open-label, parallel-group, multicenter study of matrix-induced autologous chondrocyte implantation (MACI® implant) for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea
Basad 2010(39)	MACI	Microfracture	Patients with symptomatic, post-traumatic, single, isolated chondral defects (4–10 cm^2)	Basad E, Ishaque B, Bachmann G *et al.* Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc: 18:519-527

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The literature search and further review identified two RCTs that compared MACI with MF: One was the SUMMIT trial and the other the Basad (2010) study.(39) The study by Bachmann (2004)(40) was included in the Australian MSAC submission but this abstract provides the results for a sub-group of the full cohort presented in Basad (2010). As such, only the Basad (2010) results have been included.

SUMMIT(37) is a prospective, randomised, open-label, parallel-group, multi-centre study, sponsored by Genzyme (Sanofi). The study compared MACI implant (N=72) with MF (N=72) in patients aged 18 to 55 with Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm^2. The co-primary outcomes in the trial were change from baseline to Week 104 in knee injury and osteoarthritis outcome score (KOOS) pain score and KOOS function (sports and recreational activities (SRA) score. The study was followed by a three-year extension study. Results from both studies have been included in this clinical section of the MACI submission.

The study was followed by a three-year extension study (SUMMIT extension)(38). Results from the pivotal RCT and the first year of follow-up from the three-year extension study have been included in this clinical section of the submission.

Basad *et al.* (2010)(39) compared the clinical outcomes of patients in a German clinic with symptomatic cartilage defects treated with MACI or microfracture. The study was a 2-year, randomised trial, which included patients ≥18 and ≤50 years of age with symptomatic, post-traumatic, single, isolated chondral defects (4–10 cm^2). The primary outcome measures were the Tegner, Lysholm and ICRS scores. Five-year data are likely to be published within the next 12 months however we do not have access to these data at this point.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Two other RCTs were identified which were deemed not directly relevant for the current decision problem as they did not include a comparison with MF. However, these studies have been included as supportive evidence and are described alongside 'Non-RCT evidence' in Section 5.2.7 and Section 5.8.

Table 4 Additional RCTs involving MACI

Study ID	Publications/Clinical study reports	Included in comparison of MACI and microfracture	Included as supportive evidence
Bartlett 2005(35)	Bartlett W, Skinner JA, Gooding CR, et al.: Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee. A prospective, randomised study. J Bone Jt Surg Ser B 87:640-645, 2005	No- study compares MACI and ACI	Yes- MACI single arm
Ebert 2012(18)	Ebert JR, Fallon M, Zheng MH, Wood DJ, and Ackland TR. (2012) A randomized trial comparing accelerated and traditional approaches to postoperative weight-bearing rehabilitation after matrix-induced autologous chondrocyte implantation: findings at 5 years. The American journal of sports medicine 40:1527-1537.	No- all patients received MACI implant and were then randomized to different rehabilitation programs	Yes- both MACI arms

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Ten observational or supportive comparative studies were deemed relevant as they provide evidence of the medium-term effectiveness and safety of MACI implant.

Table 5 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Bartlett 2005(35)	MACI and ACI	Patients 15 to 50 years with chondral defects sized ≥1	To compare the clinical, arthroscopic and histological outcomes of osteochondral defects in the knee treated by ACI-C or MACI in a randomised trial.	Bartlett W, Skinner JA, Gooding CR, et al.(2005) Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee. A prospective, randomised study. J Bone Jt Surg Ser B 87:640-645	Provides supportive evidence of MACI (vs ACI)
Behrens 2006(41)	MACI	Patients aged 18 to 60 years with chondral defects sized 0.64 to 17.75 cm^2	To clarify whether MACI proves suitable to treat cartilage defects and confirms objective and subjective clinical improvement up to 5 years after operation	Behrens P, Bitter T, Kurz B, and Russlies M. (2006) Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)-5-year follow-up. Knee 13:194-202.	Provides evidence of medium-term effectiveness and safety of MACI
Ebert 2011(42)	MACI	Patients aged 18 to 60 years with chondral defects sized 1.0 to 9.0 cm^2	To validate the efficacy of MACI as a suitable surgical treatment option for articular cartilage defects in the knee	Ebert JR, Robertson WB, Woodhouse J, Fallon M, Zheng MH, Ackland T, and Wood DJ. (2011) Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. The American journal of sports medicine 39:753-763.	Provides evidence of medium-term effectiveness and safety of MACI
Ebert 2012(18)	MACI	Patients aged 16 to 63 years years with chondral defect sized 0.65 to 10.0 cm2	To determine 5-year outcomes for MACI treated patients using two rehabilitation programs.	Ebert JR, Fallon M, Zheng MH et al. (2012) A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weight bearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation :	Provides evidence of medium-term effectiveness and safety of MACI with two different

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
				Findings at 5 Years. The American Journal of Sports Medicine; 40(7)	rehabilitation programs
Genovese 2011(43)	MACI	Patients aged 20 to 50 years with chondral defects ≥ 2 cm^2	To define magnetic resonance arthrography imaging findings of MACI grafts of the knee in order to describe implant behaviour and to compare findings with validated clinical scores 30 and 60 months after MACI implant	Genovese E, Ronga M, Angeretti MG, Novario R, Leonardi A, Albrizio M, Callegari L, and Fugazzola C. (2010) Matrix-induced autologous chondrocyte implantation of the knee: mid-term and long-term follow-up by MR arthrography. Skeletal radiology 40:47-56.	Provides evidence of medium-term effectiveness and safety of MACI
Marlovits 2012(44)	MACI	Patients aged 19 to 50 years with chondral defects sized >2 cm^2	To assess clinical and radiological outcomes in patients treated with the MACI procedure for symptomatic chondral defects of the knee at 5-year follow-up	Marlovits S, Aldrian S, Wondrasch B, Zak L, Albrecht C, Welsch G, Trattnig S. (2012) Clinical and radiological outcomes 5 years after matrix-induced autologous chondrocyte implantation in patients with symptomatic, traumatic chondral defects. The American journal of sports medicine 40:2273-2280.	Provides evidence of medium-term effectiveness and safety of MACI
Ventura 2012(45)	MACI (Osteochondral lesions)	Patients aged 13 to 65 years with chondral defects sized 2.0 to 10.0 cm^2	To assess the suitability of MACI for the treatment of isolated or multiple localized osteochondral defects in the knee joint	Ventura A, Memeo A, Borgo E, Terzaghi C, Legnani C, Albisetti W. Repair of osteochondral lesions in the knee by chondrocyte implantation using the MACI® technique. Knee Surg Sports Traumatol Arthrosc. 2012 Jan;20(1):121-6.	Provides evidence of medium-term effectiveness and safety of MACI
Zak 2012(46)	MACI	Patients aged 18-55 who met the	To determine if return to sport is possible 5-years	Zak L; Aldrian S, Wondrasch B (2012) Ability to Return to Sports 5 Years After	5-year evidence on the efficacy of

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
		German Societies of Traumatology and Orthopaedic Surgery regarding indications for ACI	after MACI	Matrix-Associated Autologous Chondrocyte Transplantation in an Average Population of Active Patients. The American Journal of Sports Medicine	MACI
Vijayan 2014(47)	MACI or ACI	Patients 18-48 years with symptomatic isolated chondral or osteochondral lesion > 1 cm^2 in the knee and failed ACI or MACI	To report clinical experience after failed ACI or MACI	Vijayan S, Bentley G, Rahman J et al. (2014) Revision cartilage cell transplantation for failed autologous chondrocyte transplantation in chronic osteochondral defects of the knee. Bone Joint Journal;96-B:54–8.	Provides evidence of revisional surgery after failed ACI or MACI
Nawaz 2014(48)	MACI or ACI	Patients aged 14-56 years with a symptomatic osteochondral defect range, 0.64 to 2.075 cm	To evaluate the midterm to long-term functional outcomes of 827 patients treated with ACI/MACI	Nawaz SZ, Bentley G, Briggs T *et al.* (2014) Autologous Chondrocyte Implantation in the Knee J Bone Joint Surg Am; 96:824-830	Provides medium to long-term follow-up for MACI

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 6 Comparative summary of methodology of the RCTs

Trial no. (acronym)	MACI00206 (SUMMIT)(37)	MACI00809 (SUMMIT extension)(38)	Basad (2010)(39)
Location	16 European sites	14 European sites in 7 countries	Germany
Design	Multicentre, Phase III, open-label, parallel-group RCT	Open-label extension study	Single-centre, RCT
Duration of study	2 years	3 years	2 years
Method of randomisation	After biopsies, patients were intraoperatively randomized, using an interactive voice response system and computer-generated 1:1 randomization scheme	NA	NR
Method of blinding (care provider, patient and outcome assessor)	Participants and investigators were not blinded. Histology and MRI measures were evaluated in a blinded fashion by independent experts in pathology and radiology, respectively	No blinding	NR
Intervention(s) (n =) and comparator(s) (n =)	MACI (N=72) versus microfracture (N=72)	MACI (N=65) versus microfracture (N=63)	MACI (N=39); MF (N=17)
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline to Week 104 in KOOS pain score and KOOS function (SRA) score	Change from baseline to Week 156 in KOOS pain score and KOOS function score	Tegner (activity levels), Lysholm (pain, stability, gait, clinical symptoms) and ICRS scores, measured at 8-12, 22-26 and 50-54 weeks after surgery
Secondary outcomes (including scoring methods and timings of assessments)	Response rate at 104 weeks based on KOOS pain and function (SRA) score Change from baseline to Week 104 in KOOS ADL, QoL and other symptoms. Change from baseline to Week 104 in IKDC	Response rate at Week 156 based on KOOS pain and function (SRA) score Change from MACI00206 baseline to Week 156 in	MRI scans were taken 1 week post-operatively to check for delamination and graft hypertrophy Safety was assessed by the continuous monitoring of adverse

	Change from baseline to Week 104 in SF-12 Treatment failure rate Histology ICRS II at Week 104 MRI assessment of structural repair at Week 104	KOOS pain and function, ADL, QoL MRI assessment of structural repair parameters at Week 156 Change from baseline to in IKDC at Week 156 Change from baseline to Week 156 in SF-12 Treatment failure rate	event reports
Duration of follow-up	2 years	1 year	2 years

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The inclusion and exclusion criteria for the SUMMIT and Basad (2010)(39) study are listed below. In the SUMMIT trial, initial inclusion criteria relating to the patients' KOOS score and age were applied at the screening visit. Inclusion criteria relating to patients' cartilage defects and knee health were applied during the index arthroscopy.

Table 7 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	At index visit	
MACI00206 (SUMMIT)(37)	Provided written informed consent, and was able to read and understand the language and content of the study material, understand the requirements for follow-up visits and rehabilitation, and was willing to provide required information at the scheduled evaluations	Any surgery on the knee joint within 6 months prior to Screening (not including diagnostic arthroscopy)
	Symptomatic focal cartilage defects as defined by KOOS Pain score <55	Symptomatic musculoskeletal conditions in the lower limbs that could impede measurement of efficacy for the target knee joint
	Aged ≥18 and ≤55 years	In the target knee joint, patient required or had a history of a total meniscectomy or meniscal allograft, or had a bucket handle tear or displaced tear that required a meniscectomy removing >50% of the meniscus
	Agreed to provide a blood sample at the time of cartilage biopsy during the index arthroscopy for testing of HIV-1, HIV-2, hepatitis B, hepatitis C, and syphilis	Malalignment requiring an osteotomy to correct tibial-femoral or patella-femoral alignment. Retinaculum releases were allowed if indicated to correct patella maltracking
		History of osteoarthritis (Kellgren-Lawrence Grade 3 or 4) in the target knee joint as diagnosed by clinically appropriate X-rays obtained at the Screening visit or within the previous 12 weeks
		Concomitant inflammatory disease or other condition that affected the joints (e.g., rheumatoid arthritis, metabolic bone disease, psoriasis, gout, symptomatic chondrocalcinosis)

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		History of septic arthritis in the target knee joint within 1 year prior to Screening
		Current malignancy or treatment for malignancy within the past 5 years, except non-melanoma skin cancer
		Known history of anaphylaxis to gentamicin or any of the products used in the preparation and implantation of MACI implant
		Patients who, in the opinion of the Investigator, had significant medical or psychosocial problems that warranted exclusion
		Previous investigational drug or device use within 3 months prior to Screening
		Females who were pregnant or lactating at the time of Screening
	At Screening Index Arthroscopy	
	Modified Outerbridge Grade III or IV focal cartilage defect(s) located on the femoral condyles, including the trochlea, that allowed treatment with the same surgical procedure as determined at randomisation. Note: concurrent Outerbridge Grade I and II defects were acceptable on the patella or tibia if they remained untreated (or were treated with debridement only) at the time of the arthroscopy and/or arthrotomy	Modified Outerbridge Grade III or IV defect(s) located on the patella or tibia
	Cartilage lesions determined by arthroscopy prior to randomisation and treatment with at least 1 defect size ≥3.0 cm^2 on the femoral condyles and/or the trochlea (including osteochondritis dissecans lesions that did not require a bone graft)	

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	Stable knee (i.e., anterior and posterior cruciate ligaments should be free of laxity as well as stable and intact). Ligament repair or reconstruction procedures were allowed prior to or concurrent with arthroscopy and/or arthrotomy	
	Intact meniscus or partial meniscus (≥50% of functional meniscus remaining). Meniscal repair or resection might be performed either staged or concurrent with the cartilage repair procedure provided that the surgeon was able to confirm that ≥50% of functional meniscus would remain after the corrective meniscal treatment	
MACI00809 (SUMMIT extension)(38)	Received study treatment (MACI implant or microfracture) in the MACI00206 study	None
	Provided written informed consent	
Basad (2010)(39)	Males or females ≥18 and ≤50	Presence of chronic inflammatory arthritis
	Post-traumatic, single, isolated, symptomatic chondral defects (4–10 cm^2) of the femoral condyle or patella	Instability of the knee joint
	Provided written informed consent	Prior or planned meniscectomy (≥30% of the meniscus
		BMI >30
		Varus or valgus abnormality
		Osteonecrosis, osteoarthritis and chondrocalcinosis
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

In the SUMMIT trial, patient demographic and disease characteristics at baseline were similar across treatment arms (Table 8). In both treatment groups, the majority of patients were male, and the mean age was 34.8 years in the MACI implant group and 32.9 years in the microfracture group. The duration of symptoms was a mean of 5.8yrs for the MACI group and 3.7yrs for the microfracture group. The proportion of patients with at least one prior orthopaedic knee surgery (target or non-target knee) was comparable for the two treatment groups. The median number of days since the last surgery for patients in the MACI implant group was more than twice that for patients in the MF group.

In the Basad trial, the MACI group was twice the size of the MF group due to the combining of the two MACI groups planned in the original protocol. None of the observed differences in baseline characteristics between the MF group and the MACI group was significant, except for the difference in symptom duration, which was 0.3 years longer in the MF group, which benefitted the MACI group as the outcome of repair is generally worse with a longer duration of symptoms, though the actual difference, 3-4 months, is not that long.

Table 8 Characteristics of participants in the RCTs across randomised groups

Trial no. (acronym) **Baseline characteristic**	**MACI**	**Microfracture**
MACI00206 (SUMMIT)(37)	**N=72**	**N=72**
Age (years)		
Median (range)	35.0 (18, 54)	34.0 (18, 54)
Mean (SD)	34.8 (9.16)	32.9 (8.78)
Sex, n (%)		
Male	45 (62.5)	48 (66.7)
Female	27 (37.5)	24 (33.3)
Race, n (%)		
Caucasian	72 (100)	72 (100)
Weight (kg)		
Median (range)	83.0 (52.0, 129.0)	84.0 (54.0, 134.0)
Mean (SD)	82.61 (15.07)	84.20 (15.64)
Height (cm)		
Median (range)	180.0 (150.0, 198.0)	178.0 (160.0, 199.0)
Mean (SD)	177.65 (10.35)	178.26 (8.75)
BMI (kg/cm^2)		
Median (range)	25.70 (18.9, 45.2)	26.10 (18.9, 36.3)
Mean (SD)	26.21 (4.34)	26.44 (4.03)
Prior orthopaedic knee surgery, n (%)	**65 (90.3)**	**60 (83.3%)**
Days since last surgery		
Median (range)	1476.0 (9, 12582)	685.5 (2, 7370)
Basad (2010)(36)	**N=40**	**N=20**
Gender		
Male, N (%)	25 (63)	17 (85)
Female, N (%)	15 (38)	3 (15)
Mean age (years)	33.00	37.50
Mean BMI kg/m^2 (range)	25.3 (20–34)	27.3 (24–35)
Defect cause (%)*		
Accident	8 (20)	3 (15)
Sport	19 (48)	8 (40)
Work	1 (3)	1 (5)
Daily activities	4 (10)	3 (15)
Unknown	8 (20)	5 (25)
Symptom duration (years)	2.2	2.5
Symptom onset		
Acute (<6 weeks)	14 (35)	6 (30)
Gradual (>6 weeks)	26 (65)	14 (70)
Defect location		

Trial no. (acronym) Baseline characteristic	MACI	Microfracture
Condylar	29 (73)	16 (80)
Patellar-trochlear	11 (28)	4 (20)
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The co-primary efficacy endpoint in the SUMMIT study was change in KOOS Pain and Function (SRA) scores from baseline to Week 104. The KOOS instrument is a widely accepted and validated measure of knee function. The KOOS instrument, together with MRI and histological assessment, is recommended by the FDA and EMA for the assessment of cartilage repair of the knee.(49;50) (49;51)Secondary and tertiary outcomes were response rate (defined as number of patients with at least a 10 point improvement in both KOOS scores individually (pain and function), change from baseline to 104 weeks in other KOOS domains (ADL, QOL and other symptoms), IKDC, SF-12, histology and MRI assessment. Both the IKDC and MRI are commonly used assessment measures of symptoms and function, and repair, respectively.(52;53) Outcomes assessed in the SUMMIT extension study were similar.

In the Basad study(39), the outcome measures were the Tegner (activity levels), Lysholm (pain, stability, gait, clinical symptoms) and ICRS scores. MRI scans were also taken 1 week post-operatively to check for delamination and graft hypertrophy. Safety during the study was assessed by the continuous monitoring of adverse event (AE) reports, which included description, severity, cause, action(s) taken (if any), outcome and relation (if any) to treatment in all patients enrolled.

Table 9 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
MACI00206 (SUMMIT)(37)	Change in KOOS Pain and Function (SRA) scores	The KOOS instrument is a widely accepted and validated measure of knee function.(10) (Roos and Lohmander, 2003) The KOOS instrument, together with MRI and histological assessment, is recommended by the FDA and EMA for the assessment of cartilage repair of the knee	Response rate at 104 weeks based on KOOS pain and function (SRA) score Change from baseline to Week 104 in KOOS ADL, QoL and other symptoms. Change from baseline to Week 104 in IKDC Change from baseline to Week 104 in SF-12 Treatment failure rate Histology ICRS II at Week 104 MRI assessment of structural repair at Week 104	These measures are commonly used to assess structural repair, daily functioning and quality of life. The IKDC is a validated knee-specific measure of symptoms, function, and sports activity that is appropriate for patients with a wide variety of knee problems (Irrgang et al, 2001).(52)
MACI00809 (SUMMIT extension study)(38)	Change from MACI00206 baseline to Week 156 in KOOS Pain and Function (SRA) scores	The KOOS instrument is a widely accepted and validated measure of knee function. Roos and Lohmander, 2003) (10) The KOOS instrument, together with MRI and histological assessment, is recommended by the FDA and EMA for the assessment of cartilage repair of the knee	Response rate at Week 154 based on KOOS pain and function (SRA) score Change from MACI00206 baseline to Week 156 in KOOS pain and function, ADL, QoL MRI assessment of structural repair parameters at Week 156 Change from baseline to in IKDC at Week 156 Change from baseline to Week 156 in SF-12 Treatment failure rate	These measures are commonly used to assess structural repair, daily functioning and quality of life (Irrgang et al, 2001).(52)

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Basad (2010)(36)	In the Basad study, the outcome measures were the Tegner (activity levels), Lysholm (pain, stability, gait, clinical symptoms) and ICRS scores.	The Tegner activity grading scale is a validated measure of knee function developed to complement the Lysholm scale. (54)	MRI scans were also taken 1 week post-operatively to check for delamination and graft hypertrophy. Safety during the study was assessed by the continuous monitoring of adverse event (AE) reports	MRI using specialized sequences has been shown to be a satisfactory technique for evaluating repair tissue in full-thickness traumatic defects treated by microfracture (53)

Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 10 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MACI00206 (SUMMIT)(37)	The study was designed to detect differences in the co–primary endpoints of change from baseline to year 2 for the patient's KOOS pain and function subscores for patients treated with MACI and MF	The changes from Baseline to Week 104 in KOOS Pain and Function (SRA) scores were analysed with a MANOVA model	To power the study at 85% to detect a difference between groups, a total sample size of 144 patients (72 patients per arm) was estimated based on the change from baseline to year 2 in the co–primary efficacy endpoint of the KOOS pain and function subscales with an a of .05 (and accounting for patient discontinuation), assuming a difference of 12 points each for the KOOS pain and function subscores with standard deviations of 20 and 30, respectively, and a correlation coefficient of 0.56 between the co–primary variables	Missing data was handled using last observation carried forward (LOCF) and multiple imputation (MI)
MACI00809 (SUMMIT extension study) (38)	The study was designed to examine the 5-year efficacy and safety of MACI compared with arthroscopic MF, in patients who received study treatment in study MACI00206	Change from baseline to Week 156 in KOOS Pain and Function (SRA) scores was analysed with a MANCOVA model with treatment as fixed effects and baseline KOOS Pain and Function (SRA) as covariates	There were no sample size calculations for this extension study. Sample size was based on elective participation of patients who received study treatment in the MACI00206 study. 128 patients were included in the follow-up study.	All observed data at study visits (baseline and Weeks 24, 36, 52, 78, 104 and 156) were included in this model and missing or incalculable KOOS subscale scores were imputed multiple times using a 2-step multiple imputation (MI) procedure.
Basad	The study hypothesised	For continuous outcome	Not reported	All available data (not just

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
(2010)(36)	that MACI would deliver better clinical outcomes than MF in the treatment of cartilage defects	measures, a fully non-parametric rank method was used to analyse the time courses of each of the scores. This allowed a unified longitudinal inferential analysis of the ordinal outcome measures (patient's and surgeon's ICRS scores and Tegner score) and for the (quasi-) metric Lysholm score		those from patients with complete records) were used as this analysis is able to deal with incomplete records as long as missing values can be considered "missing completely at random", which was the case

5.3.6 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In the SUMMIT trial, a post hoc sub-group analysis was undertaken. The Cochran-Mantel-Haenszel χ^2 (α=0.05) was used to analyze differences in response rates between groups by lesion size (>4 cm^2, >5 cm^2), lesion location (MFC/LFC/trochlea), and osteochondritis dissecans (OCD) etiology (yes/no).

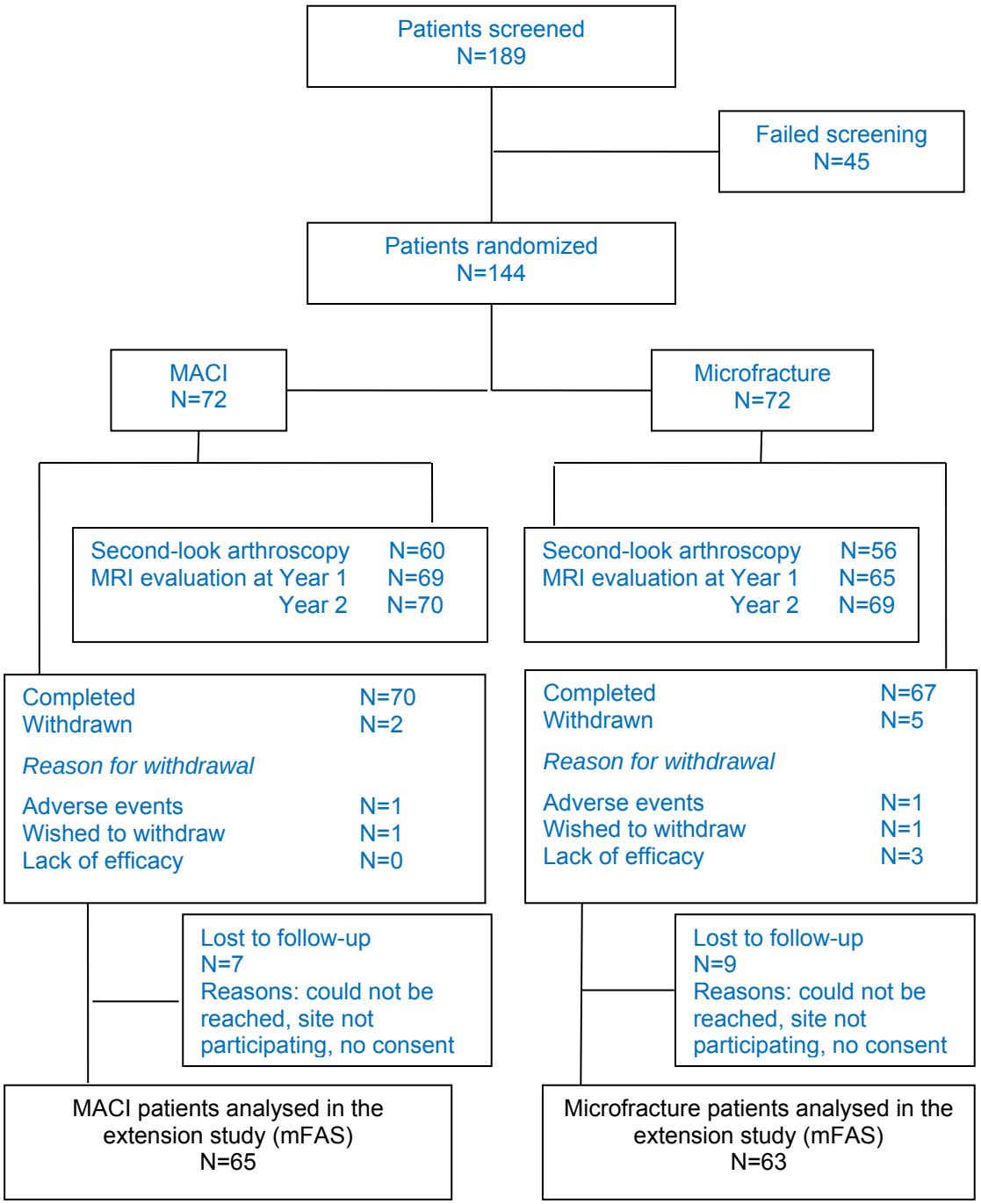
Participant flow

5.3.7 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

SUMMIT and SUMMIT extension studies

The disposition of patients from screening through to the end of 2-year follow up in the SUMMIT RCT is presented in Figure 2. Of those patients randomized to treatment in the SUMMIT trial, 65 and 63 were included in the SUMMIT 3-year extension study for MACI and MF, respectively.

Figure 2. Patient flow through the SUMMIT and SUMMIT extension trial



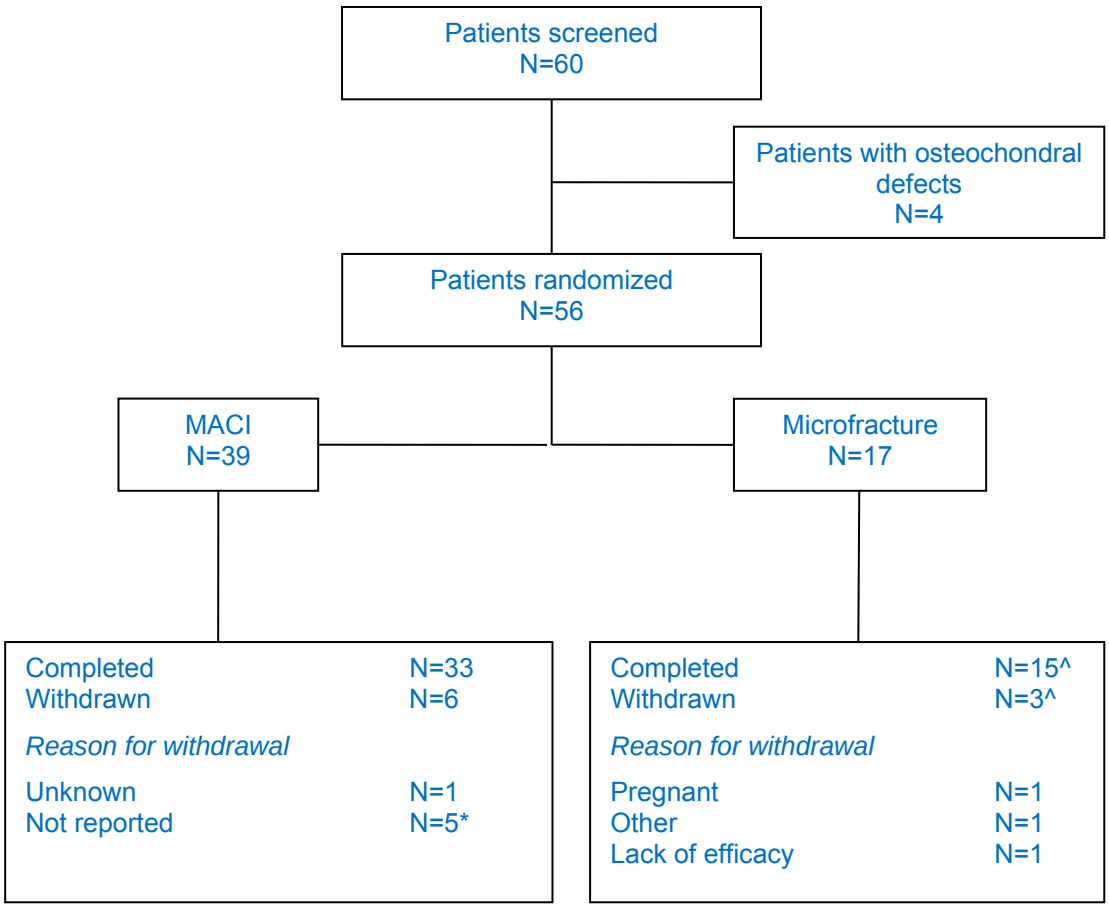
Source: Saris *et al.* 2014
Abbreviations: mFAS: modified full analysis set

Basad (2010)

The number of patients recruited and followed-up through the Basad (2010) trial is shown in **Error! Not a valid bookmark self-reference.**. Of 60 patients

randomised, 56 were randomised to treatment, 39 to MACI and 17 to Microfracture.

Figure 3. Patient flow through the Basad (2010)(36) trial



5.4 *Critical appraisal of relevant RCTs*

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- 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)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

A complete quality appraisal of the SUMMIT and Basad (2010)(36) trial are provided in Appendix 3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Table 11 Quality assessment results for RCTs

Trial no. (acronym)	SUMMIT(37)/SUMMIT extension(38)	Basad (2010)(36)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care Providers: No Participants: No Outcome Assessors: Yes	No
Were there any unexpected imbalances in drop-outs between groups?	No	No
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

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

SUMMIT

Summary

The co-primary efficacy outcome for SUMMIT was change in KOOS Pain and Function (SRA) scores from baseline to Week 104. Treatment with MACI implant resulted in a significantly greater increase in KOOS Pain and Function scores from the baseline level compared with microfracture (p=0.001). The difference in mean change in pain score was 11.76 and the mean change in function (SRA) score was 11.41. Similar results were also found for the PP analysis.

In a subgroup of patients with chondral defects sized < 4 cm^2, treatment with MACI implant resulted in a greater increase in KOOS Pain and Function score from the baseline level compared with microfracture. The difference in mean change in Pain score was 12.59 and the mean change in Function (SRA) score was 10.16.

Therefore, for the ITT and PP analyses and subpopulation of patients with defect size <4 cm^2, for the co-primary efficacy outcome, MACI implant is superior to microfracture. MACI implant was also superior to microfracture for response rate based on KOOS scores and change in other KOOS domain scores.

Primary efficacy outcomes

The co-primary efficacy outcome of the SUMMIT trial was the change in KOOS Pain and Function (SRA) scores from baseline to Week 104. The ITT analysis of KOOS Pain and Function (SRA) scores for all patients is presented in Table 12. Within each subscale, items are summed and normalised to a value between 0 (extreme problems) and 100 (no problems).

An improvement in KOOS Pain and Function (SRA) ratings was reported for patients in both treatment groups. Treatment with MACI implant resulted in a significantly greater increase in KOOS Pain and Function scores from the baseline level compared with microfracture (p=0.001). The difference in mean change in pain score was 11.76 and the mean change in function (SRA) score was 11.41. The MCID for KOOS is 10 points. Therefore, treatment with MACI implant resulted in a clinically and statistically significant improvement compared with Microfracture. Furthermore, the absolute difference between the two treatment groups at 2 and [redacted] follow up was greater than 10 points

and thus MACI patients received a MCID compared to MF patients and thus clinically significant.

Table 12 Mean change in KOOS Pain and Function (SRA) in all patients in SUMMIT (ITT[a])

	MACI	Microfracture	Difference between treatment groups
Pain			
Number of subjects [a]	72	72	
Baseline	37.00 (13.52)	35.45 (12.09)	
Week 104	82.45 (16.18)	70.85 (24.22)	
Mean change (SD)	45.45 (21.08)	35.23 (23.91)	
Adjusted [b] mean change	44.13	32.37	11.76
Function (SRA)			
Number of subjects [a]	72	72	
Baseline	14.86 (14.68)	12.57 (16.67)	
Week 104	60.90 (27.84)	48.71 (30.33)	
Mean change (SD)	46.04 (28.35)	35.83 (31.63)	
Adjusted [b] mean change	46.05	34.64	11.41
p value			0.001

Source: SUMMIT Table 10-1 pg 99
Abbreviations: MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation; SRA, sports and recreational activities
[a] Includes all randomised patients treated with MACI or microfracture
[b] Model includes treatment, study site, baseline KOOS Pain score, baseline KOOS Function (SRA) score, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location.

The PP analysis (Table 13) also showed significantly greater increases in both the KOOS Pain and Function scores for patients treated with MACI implant compared to patients treated with microfracture (p=0.001).

Table 13 Mean change in KOOS Pain and Function (SRA) in all patients in SUMMIT (PP [a])

	MACI	Microfracture	Difference between treatment groups
Pain			
Number of subjects [a]	61	65	
Baseline	36.38 (13.19)	35.90 (11.87)	
Week 104	81.15 (17.03)	71.62 (23.82)	
Mean change (SD)	44.76 (21.98)	35.73 (23.46)	
Adjusted [b] mean change	47.38	38.18	9.20
Function (SRA)			
Number of subjects [a]	61	65	
Baseline	14.43 (15.20)	12.88 (17.03)	
Week 104	59.57 (27.60)	49.77 (30.71)	
Mean change (SD)	45.14 (28.64)	36.88 (31.96)	
Adjusted [b] mean change	48.86	39.88	8.97
p value			0.001

Source: SUMMIT Table 14.2.1.2
Abbreviations: MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation; SRA, sports and recreational activities
[a] Per Protocol set was defined as those patients in the ITT set without any significant evaluability criteria violation that could possibly influence the efficacy analyses.
[b] Model includes treatment, study site, baseline KOOS Pain score, baseline KOOS Function (SRA) score, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location.

Taken together, the results from the ITT and PP analyses for the primary efficacy outcome demonstrate that patients treated with MACI implant have a significantly greater increase in both the KOOS Pain and Function (SRA) scores.

Patients with chondral defects sized < 4 cm^2

A subgroup analysis of KOOS Pain and Function (SRA) scores for patients with chondral defects sized <4 cm^2 is presented in Table 14. An improvement in KOOS Pain and Function (SRA) ratings was reported for patients in both treatment groups. Treatment with MACI implant resulted in a greater increase in KOOS pain and function score from the baseline level compared with microfracture. The difference in mean change in pain score was 12.59 and the mean change in function (SRA) score was 10.16. Therefore, in patients with

chondral defects sized <4 cm2, treatment with MACI implant resulted in a clinically significant improvement compared with microfracture.

Table 14. Mean change in KOOS Pain and Function (SRA) in patients with defects sized <4 cm^2 in SUMMIT

	MACI	Microfracture	Difference between treatment groups [c]
Pain			
Number of subjects [a]	37	40	
Baseline	37.99 (14.58)	36.18 (10.81)	
Week 104	80.48 (19.54)	66.56 (23.70)	
Mean change (SD)	42.49 (22.42)	29.90 (21.31))	12.59
Function (SRA)			
Number of subjects a	37	40	
Baseline	16.22 (15.02)	13.25 (14.96)	
Week 104	57.30 (29.41)	44.87 (30.77)	
Mean change (SD)	41.08 (27.94)	30.92 (29.15)	10.16

Source: SUMMIT additional analysis, see Appendix 2.
Abbreviations: MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation; SRA, sports and recreational activities
[a] Includes all randomised patients treated with MACI or microfracture defect size 2 to 4 cm^2
[b] Model includes treatment, study site, baseline KOOS Pain score, baseline KOOS Function (SRA) score, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location.
[c] Calculated post hoc

Secondary efficacy outcomes

Treatment response rate

A summary of the KOOS Pain and Function (SRA) response rate results is presented in Table 15. The percentage of patients who achieved a response to treatment at Week 104 was significantly greater (p=0.016) for patients in the MACI implant group compared with the microfracture group. The results were also confirmed by the unstratified analysis (p=0.011).

A subgroup analysis of KOOS Pain and Function (SRA) response rate for patients with chondral defects sized ≤ 4 cm^2 is also presented in Table 15. This analysis was consistent with the analysis of the overall trial population, showing a higher response rate for patients treated with MACI implant compared with patients treated with microfracture.

Taken together, the results of the KOOS responder analysis support the clinical claim that, in patients with chondral defects sized ≤4 cm^2, MACI implant is superior to microfracture.

Table 15 KOOS Response rate [a] in all patients in SUMMIT (ITT [b])

N (%)	MACI (n=72)	Microfracture (n=72)	p value [c]
All patients			
Stratified by centre			
Responded	63 (87.5)	49 (68.1)	0.016
Not responded	9 (12.5)	20 (27.8)	
Missing	0	3 (4.2)	
Unstratified			
Responded	62 (86.1)	48 (66.7)	0.011
Not responded	7 (9.7)	18 (25.0)	
Missing	3 (4.2)	6 (8.3)	
Patients with defects sized ≤4 cm^2			
N (%)	MACI (n=37)	Microfracture (n=41)	p value [c]
Responded	29 (78.38)	25 (60.98)	NR
Not responded	8 (21.62)	13 (31.71)	
Missing	0	3 (7.32)	

Source: SUMMIT Table 10-5 pg 106 and additional analysis, see Appendix 2.
Abbreviations: ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; NR, not reported; SRA, sports and recreational activities
[a] KOOS Response Rate: a patient is regarded as a responder for KOOS if a 10-point improvement in both KOOS Pain and Function (SRA) scores was achieved with respect to Baseline. Otherwise, the patient is regarded as a non-responder.
[b] Includes all randomised patients treated with MACI or microfracture
[c] P-value: calculated for response categories 'Responded' and 'Not responded' using a CMH $\chi 2$ Test (α=0.05) to compare between treatment groups

Change in KOOS ADL, QOL and Other symptoms from Baseline to Week 104

A summary of the other KOOS subscale results (ADL, QOL, and Other Symptoms) is presented in. Improvement in ratings of ADL, QOL, and Other Symptoms was reported for patients in both treatment groups from Baseline to Week 104. The improvements for all 3 KOOS subscales were significantly greater for patients in the MACI implant group compared with the microfracture group in ADL ($p<0.001$), QOL ($p=0.029$), and Other Symptoms ($p<0.001$). These results are consistent with the results for the primary

efficacy outcome and support the claim that MACI implant is superior to microfracture.

Table 16 Mean change in KOOS ADL, QOL and Other symptoms in all patients in SUMMIT (ITT [a])

	MACI	Microfracture	Difference between treatment groups
ADL			
Number of subjects [a]	72	72	
Baseline	43.51 (18.15)	42.57 (19.55)	
Week 104	87.21 (16.47)	75.75 (24.21)	
Mean change (SD)	43.70 (24.52)	32.76 (26.78)	
Adjusted [b] mean change	42.39	30.38	12.01
p value			<0.001
QOL			
Number of subjects [a]	72	72	
Baseline	18.75 (14.65)	17.19 (14.06)	
Week 104	56.16 (23.91)	47.27 (26.99)	
Mean change (SD)	37.41 (27.24)	29.93 (28.11)	
Adjusted [b] mean change	38.00	29.03	8.98
p value			0.029
Other symptoms			
Number of subjects [a]	72	72	
Baseline	48.26 (16.85)	44.39 (18.58)	
Week 104	83.73 (13.98)	72.23 (19.47)	
Mean change (SD)	35.47 (20.83)	27.31 (24.59)	
Adjusted [b] mean change	34.37	22.76	11.61
p value			<0.001

Source: SUMMIT Table 10-6 pg 108-109
Abbreviations: ADL, activities of daily living; ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; QOL, knee-related quality of life; SD, standard deviation
[a] Includes all randomised patients treated with MACI or microfracture
[b] least-squares adjusted means

Change in International Knee Documentation Committee (IKDC) subjective knee evaluation from Baseline to Week 104

The IKDC Subjective Knee Evaluation Form is a validated knee-specific measure of symptoms, function, and sports activity. A summary of the change from baseline in IKDC subjective knee evaluation scores is presented in Table

17. From Baseline to Week 104, patients in both treatment groups had increases in their IKDC scores. A strong trend towards a significantly greater mean improvement in knee function from Baseline to Week 104 was shown for patients in the MACI implant group compared with the microfracture group (p=0.069).

Table 17. Mean change in IKDC in all patients in SUMMIT (ITT [a])

	MACI	Microfracture	Difference between treatment groups
Number of subjects [a]	72	72	
Baseline	32.87 (13.28)	29.29 (13.43)	
Week 104	65.74 (18.52)	58.84 (22.28)	
Mean change (SD)	32.94 (21.87)	29.31 (23.81)	
Adjusted [b] mean change	32.65	26.71	5.94
p value			0.069

Source: SUMMIT Table 10-7 pg 112
Abbreviations: IKDC, international knee documentation committee; ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation
[a] Includes all randomised patients treated with MACI or microfracture
[b] least-squares adjusted means

Change in SF-12 from Baseline to Week 104

The SF-12 was used to measure health-related quality of life in the SUMMIT trial. A summary of the change in SF-12 Physical and Mental Component Scores, transformed into z-scores, is presented in Table 18 . From Baseline to Week 104, patients in both treatment groups had substantial increases in their Physical and Mental Component Scores. There was no significant difference between treatment groups in the improvement in the Mental Component Score (p=0.523). In contrast, patients who were treated with MACI implant experienced significantly greater improvements in their Physical Component Score compared with patients treated with microfracture (p=0.001). This result underlines the superior improvements in physical well-being achieved by treatment with MACI implant.

Table 18 Mean change in SF-12 scores in all patients in SUMMIT (ITT a)

	MACI	Microfracture	Difference between treatment groups
Physical Component Score			
Number of subjects [a]	72	72	
Baseline	-1.77 (0.86)	-1.93 (0.82)	
Week 104	-0.32 (0.89)	-0.82 (1.12)	
Mean change (SD)	1.45 (1.20)	1.06 (1.21)	
Adjusted [b] mean change	1.53	1.02	0.51
p value			0.001
Mental Component Score			
Number of subjects [a]	72	69	
Baseline	0.04 (1.16)	-0.17 (1.30)	
Week 104	0.45 (0.87)	0.49 (1.00)	
Mean change (SD)	0.41 (1.06)	0.63 (1.39)	
Adjusted [b] mean change	0.44	0.53	-0.09
p value			0.523

Source: SUMMIT Table 10-7 pg 112-113
Abbreviations: ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation; SF-12; 12-Item short-form health survey
[a] Includes all randomised patients treated with MACI or microfracture
[b] least-squares adjusted means

MRI at Week 104

MRI assessments of structural repair parameters at baseline and Week 104 were used to assess the degree of defect fill based on the thickness of repair tissue. The results of the analysis for MRI Degree of Defect Fill are presented in Table 19. At Week 104, improvement since study treatment in defect fill was evident for patients in both treatment groups. The defects were filled to more than 50% for the majority of patients and the proportion of patients with >75% defect fill was comparable between patients treated with MACI implant or microfracture. There was no significant difference between the treatment groups in MRI Degree of Defect Fill at Week 104.

Table 19. MRI degree of defect fill at Week 104 for all patients in SUMMIT (ITT a)

Number of patients with degree of defect fill	MACI n (%)	Microfracture n (%)	P value
76 to 100%	35 (48.6)	41 (56.9)	0.920
51 to 75%	23 (31.9)	12 (16.7)	
26 to 50%	4 (5.6)	7 (9.7)	
0 to 25%	8 (11.1)	9 (12.5)	
Measurement of agreement Weighted Kappa			0.571
95% CI			0.421, 0.722

Source: SUMMIT Table 10-4 pg 105

Abbreviations: CI, confidence interval; ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; MRI, magnetic resonance imaging

[a] Includes all randomised patients treated with MACI or microfracture

Histology ICRS II assessment at Week 104

The quality of the cartilage repair was assessed using the ICRS II histology scoring system. The results of the "Overall Assessment" component of the ICRS II score are shown in Table 20 The mean ICRS II Overall Assessment score at Week 104 was comparable for the MACI implant and microfracture groups and there was no significant difference (p=0.717) between the treatment groups.

Table 20. Microscopic ICRS II overall assessment at Week 104 for all patients in SUMMIT (ITT [a])

	MACI	Microfracture	Difference between treatment groups
Number of subjects [a]	60	56	
Mean (SD)	64.3 (22.34)	64.3 (22.34)	
Adjusted [b] mean	63.82	62.31	1.52
p value			0.717

Source: SUMMIT Table 10-3 pg 103

Abbreviations: ITT, intention to treat; MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation

[a] Includes all randomised patients treated with MACI or microfracture

[b] least-squares adjusted means

SUMMIT extension study

Co primary efficacy outcomes

Secondary efficacy outcomes

The results for secondary efficacy outcomes assessed at Week 156 were similar to those assessed at Week 104, illustrating that MACI remained superior to microfracture at 3-year follow-up (Table 21).

Table 21. Secondary efficacy outcomes at Week 104 and Week 156

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Basad (2010){14)

Summary

The difference between baseline and 24 months post-operatively for both treatment groups was significant for the Lysholm, Tegner, patient ICRS and surgeon ICRS scores (P<0.0001). However, MACI was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm (P = 0.005), Tegner (P = 0.04), ICRS patient (P = 0.03) and ICRS surgeon (P = 0.02) scores. There were no safety issues related to MACI or MF during the study. Therefore MACI was considered superior to MF in the treatment of articular defects over 2 years.

Mean Lysholm score

The mean Lysholm score in the MACI group improved from 52 at baseline to 95 at 12 months. This improvement was broadly maintained at 24 months (mean score 92). In the MF group, these scores improved from 55 at baseline to 81 at 12 months but then declined to 69 at 24 month (Table 22). Individual

patients' Lysholm scores showed maintained improvement over 2 years in the patients treated with MACI, but patients treated with MF showed a much broader scattering of results. The difference between baseline and 24 months post-operatively for both treatment groups was significant (P<0.0001), but MACI was significantly more effective over time than MF (P = 0.005).

Table 22. Mean and median lysholm scores over time

	Baseline	3 months	6 months	12 months	18 months	24 months
Mean MACI	52 ± 26	77 ± 17	87 ± 17	92 ± 11	91 ± 13	92 ± 9
Median MACI	58	81	93	95	93	94
N MACI	39	39	39	38	32	33
Mean MF	55 ± 25	66 ± 20	82 ± 18	82 ± 22	80 ± 22	69 ± 26
Median MF	56	70	88	90	90	70
N MF	17	17	17	17	17	15

Source: Basad 2009, Table 2

The median Tegner score improved from level 2 at baseline to level 4 at 12 months in the MACI group, and this improvement was maintained at 24 months. The median Tegner scores improved from level 2 at baseline to level 3 at 12 months in the MF group, and this improvement was maintained at 24 months (Table 23). The difference between baseline and 24 months post-operatively for both treatment groups was significant (P<0.0001), but MACI was significantly more effective over time than MF (P = 0.04).

Table 23. Disposition of Tegner score levels and medians over time

	MACI				MF			
	Baseline	6 months	12 months	24 months	Baseline	6 months	12 months	24 months
N	39	39	37	37	20	18	18	17
Level 10	0	0	0	0	0	0	0	0
Level 9	0	0	0	0	0	0	0	0
Level 8	1	0	0	0	0	0	0	0
Level 7	0	1	1	0	0	0	0	0
Level 6	1	0	3	2	0	0	0	0
Level 5	1	1	5	7	0	1	1	1
Level 4	1	10	11	16	1	3	6	6
Level 3	11	24	15	11	6	13	9	8
Level 2	12	2	2	1	5	1	1	1
Level 1	12	1	0	0	8	0	1	1

Level 0	0	0	0	0	0	0	0	0
Median	Level 2	Level 3	Level 4	Level 4	Level 2	Level 3	Level 3	Level 3

Source: Basad 2009, Table 3

The number of completers by ICRS score, by therapy, over time is shown in. The difference between ICRS patient scores at baseline and 24 months post-operatively was significant for both treatment groups (P<0.0001), but MACI was significantly more effective over time than MF (P = 0.03). For the surgeon's ICRS scores, the difference between baseline and 24 months post-operatively was significant for both treatment groups (P<0.0001). MACI was significantly more effective over time than MF (P = 0.02).

Table 24. Disposition of ICRS scores, by therapy over time

ICRS score	Therapy	Baseline	3 months	6 months	12 months	18 months	24 months
I	MACI	2	5	7	18	11	14
	MF		1		4	2	2
II	MACI	4	17	22	14	15	14
	MF	3	5	12	9	8	4
III	MACI	21	13	6	2	3	2
	MF	10	9	3	3	2	3
IV	MACI	8					
	MF	2				1	1

Source: Basad 2009, Table 4

5.6 *Meta-analysis*

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No meta-analysis was undertaken.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

NA

5.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact

that each exclusion has on the overall meta-analysis should be explored.

5.7 *Indirect and mixed treatment comparisons*

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

An indirect comparison of MACI versus ACI and MACI versus mosaicplasty was undertaken as part of the MSAC submission for MACI in Australia in January 2013. As there was no time to update the indirect comparison, we report the story carried out for the MSAC here.

A full review of the literature was undertaken at that time to identify all randomised trials evaluating the efficacy of MACI implant, ACI, microfracture and mosaicplasty treatments for patients with chondral defects of the knee. These trials would be used in conjunction with the pivotal SUMMIT trial to provide evidence for the clinical efficacy of each of the interventions.

The following approaches were used to search for relevant data:

- a search of published literature using the electronic database EMBASE.com, which allows concurrent searching of EMBASE and MEDLINE

- a search of the Cochrane Library and other health technology assessment websites

The search strategies used are summarised in Appendix 4. After reviewing the retrieved references, a manual search of the reference lists of relevant articles was performed. A total of 756 citations were retrieved, including 605 citations from EMBASE.com and 151 citations from the Cochrane library

5.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Table 25. Summary of identification of randomised trials from the search of the published literature

	EMBASE (incorporates MEDLINE)	The Cochrane Library
Number of citations retrieved by search	606	151
Number of citations excluded after title / abstract review		
• Duplicate citation	6	28
• Not a fully published study	1	21
• Wrong study type: not a randomised trial	434	12
• Wrong intervention: not MACI, ACI, microfracture or mosaicplasty	70	72
• Wrong population: not human adults with chondral defects of the knee	70	12
• Wrong comparator: not one of MACI, ACI, microfracture or mosaicplasty compared with another	9	0
• Not English language	2	6
Total number of citations excluded	592	151
Total number of studies identified for full text review		14

Abbreviations: ACI, autologous chondrocyte implant; MACI, matrix-induced autologous chondrocyte implant;

Further details of the selection of included studies are provided below.

Systematic reviews of cartilage repair techniques

The literature search described above identified 14 relevant systematic reviews or technology assessment reports that included an assessment of MACI implant, ACI, microfracture or mosaicplasty (Table 26). The reference list of each review was cross checked with the citations identified from the literature search. None of the systematic reviews included any additional studies other than those already identified in the literature search at the time. Additionally, a recently completed randomised trial of MACI implant (SUMMIT) was not included in any of the systematic reviews.

Table 26. Systematic reviews containing MACI implant, ACI, microfracture or mosaicplasty

Systematic review / HTA report
Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, Jobanputra P, and Waugh N. (2005) Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: Systematic review and economic evaluation. Health Technology Assessment 9:iii-48.
Harris JD, Siston RA, Brophy RH, Lattermann C, Carey JL, and Flanigan DC. (2011) Failures, re-operations, and complications after autologous chondrocyte implantation: a systematic review (Provisional abstract). Osteoarthritis. and Cartilage. 19:779-791.
Jobanputra P, Parry D, Fry SA, and Burls A. (2001) Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review (Structured abstract). Health Technology Assessment. 5:1-57.
Jobanputra P, Parry D, Meads C, and Burls A. (2001) Autologous chondrocyte transplantation for cartilage defects in the knee joint (Structured abstract). Birmingham. : West Midlands. Health Technology Assessment. Collaboration.88.
Kon E, Verdonk P, Condello V, Delcogliano M, Dhollander A, Filardo G, Pignotti E, and Marcacci M. (2009) Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee: systematic clinical data review and study quality analysis. The American journal of sports medicine 37 Suppl 1:156S-166S.
Magnussen RA, Dunn WR, Carey JL, and Spindler KP. (2008) Treatment of focal articular cartilage defects in the knee: a systematic review (Structured abstract). Clinical. Orthopaedics. and Related. Research. 466:952-962.
Mithoefer K, McAdams T, Williams RJ, Kreuz PC, and Mandelbaum BR. (2009) Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis (Structured abstract). American. Journal of Sports Medicine 37:2053-2063.
Naveen S, Robson N, and Kamarul T. (2012) Comparative analysis of autologous chondrocyte implantation and other treatment modalities: a systematic review (Provisional abstract). Database of Abstracts. of Reviews of Effects.89-96.
NICE (2008) The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints: review of technology appraisal 16. Technology appraisal 89
Swedish-Council-on-Technology-Assessment-in-Health-Care. (2000) Autologous chondrocyte transplantation in treating cartilage damage in the knee - early assessment briefs (ALERT) (Brief record). Stockholm. : Swedish. Council. on Technology Assessment. in Health Care.
Vasiliadis HS and Wasiak J. (2010) Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. Cochrane database of systematic reviews (Online)CD003323.
Vasiliadis HS, Wasiak J, and Salanti G. (2010) Autologous chondrocyte implantation for the treatment of cartilage lesions of the knee: A systematic review of randomized studies. Knee Surgery, Sports Traumatology, Arthroscopy 18:1645-1655.
Vavken P and Samartzis D. (2010) Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: A systematic review of controlled trials. Osteoarthritis and Cartilage 18:857-863.
Wasiak J, Clar C, and Villanueva E. (2006) Autologous cartilage implantation for full thickness articular cartilage defects of the knee. Cochrane database of systematic reviews (Online) 3:CD003323.

Abbreviations: HTA, Health Technology Assessment; NICE, National Institute for Clinical Excellence

Selection of included studies

A total of 14 randomised studies were reviewed in full text. The process of the full text review is described below and a summary is presented in Table 27.

The pivotal SUMMIT trial reported a responder analysis based on the KOOS score for MACI implant compared to microfracture. The clinical outcomes reported in each of the remaining randomised studies were reviewed. In order to be eligible for inclusion, the study must report a responder analysis based on the KOOS score. One study of ACI compared with microfracture{Saris, 2009 105 /id} that reported a KOOS responder analysis was identified. The combination of the SUMMIT trial and Saris 2009 were selected to provide evidence for the efficacy of MACI implant, ACI and microfracture.

There were no studies of mosaicplasty that reported a responder analysis based on the KOOS score. For mosaicplasty, the Modified Cincinnati Knee Score was selected as a proxy for a KOOS responder analysis. The adaptation of the Modified Cincinnati Knee Score for use in the economic model is described in later sections. Each of the studies containing a mosaicplasty treatment arm was reviewed and those that did not report the Modified Cincinnati Knee Score were excluded. Two publications from one study(30;55) reported the Modified Cincinnati Knee Score. The Bentley 2012(56) publication was excluded as the study duration of 10 years was not comparable to the SUMMIT trial 2-year duration. The Bentley 2003(30) publication was selected for inclusion, at the time of the Australian submission. If we had redone the indirect comparison, the Bentley 2012 (56) study would not have been excluded, as this demonstrates the longevity of the MACI/ACI implants.

Table 27. Summary of the selection process for included studies

Total number of studies identified for full text review	**14**
Number of citations excluded after full text review	
• Trial does not contain a KOOS responder analysis (MACI, ACI and microfracture studies)	7
• Trial does not contain the Modified Cincinnati Knee (mosaicplasty studies only)	4
• Trial duration was not comparable to SUMMIT trial (2 years)	1
Total number of citations excluded	12
Total number of included studies	**2**

Abbreviations: ACI, autologous chondrocyte implant; KOOS, knee injury and osteoarthritis outcome score; MACI, matrix-induced autologous chondrocyte implant;

Following the completion of the full text review process, two studies, Bentley 2003(30) and Saris 2009(57), were selected for inclusion together with the SUMMIT trial. The citation for each of the included studies is presented in Table 28, below.

Table 28. List of included studies

Study ID	**Citations of included studies**
SUMMIT (MACI00206)(37)	A Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study to Demonstrate the Superiority of Matrix-induced Autologous Chondrocyte Implantation (MACI® implant) versus Arthroscopic Microfracture for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle including the Trochlea.
Bentley 2003(30)	Bentley G, Biant LC, Carrington RWJ, Akmal M, Goldberg A, Williams AM, Skinner JA, and Pringle J. (2003) A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. Journal of Bone and Joint Surgery - Series B 85:223-230.
Saris 2009(57)	Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, and Luyten FP. (2009) 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. The American journal of sports medicine 37 Suppl 1:10S-19S.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Characteristics of included studies

A brief summary of key trial characteristics for the SUMMIT trial, Bentley 2003(30) and Saris 2009(57) is presented in Table 29. SUMMIT was a prospective, randomised, open-label, parallel-group, multicentre study. The study compared MACI implant (N=72) with microfracture (N=72) in patients aged 18 to 55 with Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm2. Primary outcomes in the trial were change from baseline to Week 104 in knee injury and osteoarthritis outcome score (KOOS) pain score and KOOS function (sports and recreational activities (SRA) score. Secondary outcomes were response rate (defined as number of patients with at least a 10 point improvement in KOOS pain and function), change from baseline to 104 weeks in other KOOS domains (activities of daily living (ADL), knee-related quality of life (QOL) and other symptoms), international knee documentation committee (IKDC) subjective knee evaluation form, 12-Item Short-Form Health Survey (SF-12), histology and magnetic resonance imaging (MRI) assessment.

Bentley 2003(30) was an RCT conducted at a single hospital in the United Kingdom. The trial enrolled 100 consecutive patients with symptomatic chondral defects of the knee who were randomised to treatment with either ACI (N=58) or mosaicplasty (N=42). The mean size of the patients' chondral defect was 4.66 cm2 and the range was 1 cm2 to 12.2 cm2. The study assessed treatment efficacy at two years post-surgery using the Modified Cincinnati Knee and Stanmore functional rating scores. The quality of the cartilage repair was assessed by ICRS grading and histology.

Saris 2009(57) was a multicentre RCT conducted at 13 centres in Belgium, Croatia, Germany and the Netherlands. The study enrolled patients aged between 18 and 50 years with a single chondral defect of the knee sized between 1 cm2 and 5 cm2. Patients were randomised to receive either ACI (ChondroCelect) or microfracture and were followed-up after three years. Clinical efficacy was assessed using the KOOS instrument, with the results expressed as both change from baseline and as a dichotomised responder analysis. The study also used a visual analogue scale to assess efficacy and reported the rate of treatment failure and MRI assessment of repair quality.

Table 29 Summary of the characteristics of the included clinical trials

Study ID	Study design	Study population characteristics	Compared interventions (N)	Clinical outcomes
SUMMIT(37)	Multicentre, Phase III, open-label, parallel-group RCT, 2-year follow-up	Patients aged 18 to 55 years, with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm^2.	MACI implant (N=72) versus microfracture (N=72)	• Change from baseline to Week 104 in KOOS pain score and KOOS function (SRA) score. • Response rate at 104 weeks based on KOOS pain and function (SRA) score • Change from baseline to Week 104 in KOOS ADL, QOL and other symptoms. • Change from baseline to Week 104 in IKDC • Change from baseline to Week 104 in SF-12 • Treatment failure rate • Histology ICRS II at Week 104 • MRI assessment of structural repair at Week 104
Bentley 2003(30)	Single centre, open-label, RCT, 2-year follow-up	100 consecutive patients aged 16-49 with symptomatic chondral defects of the knee; mean defect size 4.66 cm^2	ACI (N=58) versus mosaicplasty (N=42)	• Modified Cincinnati Knee (Excellent/Good/Fair/Poor) • Stanmore functional rating score • ICRS grading • Histology
Saris 2009(57)	Multicentre, open-label, parallel-group RCT, 3-year follow-up	Patients aged 18 to 50 years, with single ICRS grade III/IV symptomatic cartilage lesion of the femoral condyles sized 1-5 cm^2	ACI (ChondroCelect) (N=57 randomised; 51 treated) versus microfracture (N=61)	• Change from baseline in KOOS • KOOS responder analysis • Visual analogue scale • Treatment failure rate • Magnetic resonance Observation of Cartilage Repair Tissue (MOCART)

Abbreviations: ADL, activities of daily living; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, knee injury and Osteoarthritis Outcome score; MACI; matrix-induced autologous chondrocyte implant; MOCART, Magnetic resonance Observation of Cartilage Repair Tissue; MRI, magnetic resonance imaging; NA, not applicable; QOL, knee-related quality of life; RCT, randomised control trial; SF-12, 12-Item Short-Form Health Survey; SRA, sports and recreational activities.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

No studies that directly compared MACI implant and ACI using a KOOS responder analysis were identified. Consequently, to estimate the comparative effectiveness of MACI implant and ACI, an indirect comparison via microfracture was performed. The indirect comparison used the following data:

- KOOS response rates from the SUMMIT trial (MACI implant versus microfracture)
- KOOS response rates from the Saris 2009(57) (ACI versus microfracture)

The KOOS instrument is a widely accepted and validated measure of knee function and includes the following 5 separately scored subscales which in total addressed 42 items:

- Pain (9 items)
- Function (SRA) (5 items)
- Function in Activities of Daily Living (ADL; 17 items)
- Knee-Related Quality of Life (QOL; 4 items)
- Other Symptoms (e.g. swelling, restricted range of motion [7 items])

A 5-point Likert scale was used to record the response to each item ranging from 0 (no problems) to 4 (extreme problems). Within each subscale, items are summed and normalised to a value between 0 (extreme problems) and 100 (no problems). A level of 10 points or more of improvement or decline represents the minimum clinically important difference (MCID).(10)

The results from the KOOS assessment were used to assess whether patients had responded to treatment. A responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from baseline, based on the MCID for the KOOS instrument.(10)

The definition of response used in the SUMMIT trial was different to the definition of response used in the Saris 2009 study, although both were based on results from the KOOS instrument.

The analyses presented in Saris 2009 included all patients who had undergone assessments at 36 months. To be consistent with the SUMMIT trial, a post hoc ITT analysis of the Saris 2009 data was also conducted. The ITT analysis included all patients who received ACI or microfracture treatment, with missing subjects classed as non-responders.

To ensure consistency, the results from the SUMMIT trial were also reanalysed using the definition of response from Saris 2009, which was:

- "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".

The authors of the Saris 2009 study note that the Function (SRA) domain was excluded from their KOOS analysis because of the large amount of missing data for this subdomain. This was taken into account in reanalysis of the SUMMIT trial data.

The literature search did not identify any randomised trials of mosaicplasty that reported a response rate based on the KOOS score. The literature search identified one randomised study comparing ACI and mosaicplasty that reported the results from the Modified Cincinnati Knee score in four categories: 'excellent', 'good', 'fair' and 'poor'.(30) These data have been used to create a proxy response rate, with patients who experienced an 'excellent' or 'good' results being classed as responders and patients who had a 'fair' or 'poor' result being classed as non-responders.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Though it was not explicitly reported, the indirect comparison of MACI and ACI was undertaken using the Bucher method.

5.7.6 Please present the results of the analysis.

MACI versus ACI

The analyses presented in Saris 2009(57) included all patients who had undergone assessments at 36 months. To be consistent with the SUMMIT trial, a post hoc ITT analysis of the Saris 2009 data was also conducted. The ITT analysis included all patients who received ACI or microfracture treatment, with missing subjects classed as non-responders.

The results from the Saris 2009 study are presented in Table 30. In both analyses the proportion of patients who responded to treatment was higher in the ACI group; however, this trend did not reach statistical significance.

Table 30 KOOS Response rate at 36 months in Saris 2009

N (%)	ACI	Microfracture	p value [c]
Saris 2009			
Number of patents	41	50	0.084
Responded	34 (83)	31 (62)	
Not responded [a]	7 (17)	19 (38)	
Saris 2009 ITT [b]			
Number of patients	51	61	0.09
Responded	34 (67)	31 (51)	
Not responded	17 (33)	30 (49)	

Source: Saris 2009 p15S.
Abbreviations: ACI, autologous chondrocyte implant; ITT, intention to treat; NR, not reported
a Includes patients with no clinically relevant change or worse response.
b All values calculated post hoc
c P value for ITT analysis calculated post hoc in ReviewManager 5.

The results from Saris 2009 were combined with those from the SUMMIT trial in an indirect comparison of MACI implant compared with ACI. It should be noted that the SUMMIT trial and Saris 2009 had different durations. This may affect the results of the indirect comparison and should be considered when interpreting the results. The majority of the response to treatment for both ACI and MACI implant occurs soon after treatment, thus the difference in duration between the 2-year SUMMIT trial and the 3-year Saris 2009 study may have only a minimal effect on the analysis.

The analysis of the efficacy of MACI implant compared with ACI consists of four indirect comparisons based on the available data. These analyses

included the data as reported in SUMMIT and Saris 2009 as well as the re-analysed SUMMIT response rate and the post hoc ITT analysis of Saris 2009. The four indirect comparisons included here are:

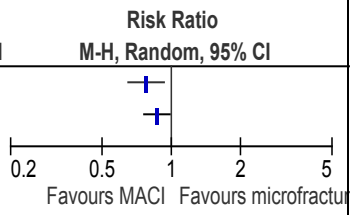
1. SUMMIT vs. Saris 2009
2. SUMMIT vs. Saris 2009 ITT
3. SUMMIT reanalysis vs. Saris 2009
4. SUMMIT reanalysis vs. Saris 2009 ITT

The results of each comparison are presented in Figure 4 below. Overall the analyses showed no significant difference between ACI and MACI in the likelihood of achieving a response to treatment.

Figure 4. ACI versus MACI implant via microfracture: KOOS response rates

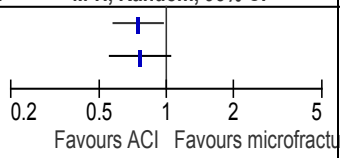
MACI implant versus microfracture

Study or Subgroup	Microfracture Events	Microfracture Total	MACI Events	MACI Total	Weight	Risk Ratio M-H, Random, 95% CI
SUMMIT	49	72	63	72		0.78 [0.65, 0.93]
SUMMIT reanalysis	58	72	67	72		0.87 [0.76, 0.99]



ACI versus microfracture

Study or Subgroup	Microfracture Events	Microfracture Total	ACI Events	ACI Total	Weight	Risk Ratio M-H, Random, 95% CI
Saris 2009	31	50	34	41		0.75 [0.58, 0.97]
Saris 2009 ITT	31	61	34	51		0.76 [0.56, 1.04]



ACI versus MACI via microfracture:

Analysis 1: SUMMIT vs. Saris 2009

RR 1.040 (0.762, 1.420)

Analysis 2: SUMMIT vs. Saris 2009 ITT

RR 1.026 (0.716, 1.470)

Analysis 3: SUMMIT reanalysis vs. Saris 2009

RR 1.160 (0.870, 1.547)

Analysis 4: SUMMIT reanalysis vs. Saris 2009 ITT

RR 1.145 (0.815, 1.607)

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

MACI implant versus mosaicplasty

Results

The results from the Bentley 2003(30) study are presented in Table 31. Overall, 88% of patients treated with ACI and 69% of patients treated with mosaicplasty had an 'excellent' or 'good' Modified Cincinnati Knee assessment at 12 months. For the purposes of the economic model, these patients have been classed as responders. Based on this analysis, patients

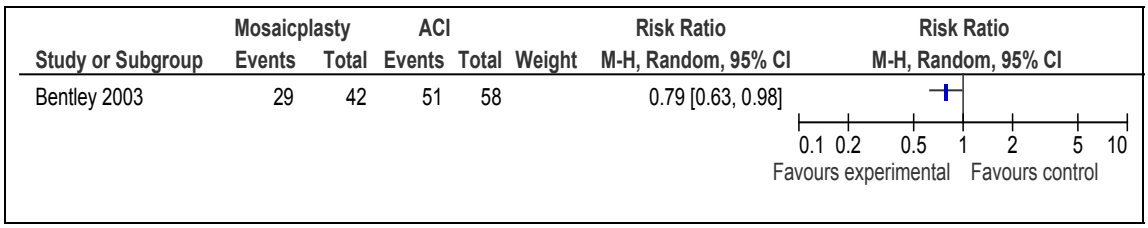
treated with ACI are significantly more likely to achieve a response to treatment than patients treated with mosaicplasty (p=0.03).

Table 31 Modified Cincinnati Knee rating at 12 months in Bentley 2003

N (%)	ACI	Mosaicplasty	p value [a]
Bentley 2003(30)			
Number of patients	58	42	0.03
Responder: 'excellent' or 'good'	51 (88)	29 (69)	
Non-responder: 'fair' or 'poor'	7 (12)	13 (31)	

Source: Bentley 2003 p226.
Abbreviations: ACI, autologous chondrocyte implant
a P value for ITT analysis calculated post hoc in ReviewManager 5.
A relative risk analysis of the post hoc responder analysis of Bentley 2003 is presented graphically in Figure 5. The analysis shows that patients treated with mosaicplasty have a significantly lower likelihood of achieving a response compared with patients who received ACI (RR 0.79).

Figure 5. Difference in Modified Cincinnati Knee response rates for mosaicplasty relative to ACI



Abbreviations: ACI, autologous chondrocyte implant; CI, confidence interval; M-H, Mantel-Haenszel.

Previous analyses have established that there is no significant difference in treatment response rate between ACI and MACI implant. Consequently, it can be concluded that the response rate for mosaicplasty relative to ACI can also be applied to mosaicplasty relative to MACI implant. Therefore MACI can be considered more efficacious than mosaicplasty.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

NA

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

NA

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

NA

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Identification and selection of studies

As discussed in Section 5.2.7, a search for observational studies was also undertaken as part of the Australian MSAC submission. The same search strategy was used as for the identification of randomised trials (Appendix 2). Embase, Medline, The Cochrane Library, and the Sponsor's databases were

searched with the aim to identify fully published English language observational studies of MACI implant with durations greater than two years. Any studies that did not provide both a baseline and post-baseline measurement for the reported clinical outcomes were excluded. This search identified five relevant studies. Two of these, Bartlett (2005)(35) and Ebert (2011 and 2012)(18;42), were randomised trials but have been included as supportive evidence here. Only the results of the MACI arm are considered from the Bartlett trial and for the Ebert trials all patients received MACI, but were randomised to different rehabilitation regimens.

A further targeted search was undertaken for this submission based on known publications and an additional five studies were considered relevant for inclusion. A list of observational and supportive studies examining MACI is provided in Table 32.

Table 32. Observational studies relevant to the decision problem

Study ID	Publications
Bartlett 2005(35)	Bartlett W, Skinner JA, Gooding CR, *et al.(*2005) Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee. A prospective, randomised study. J Bone Jt Surg Ser B 87:640-645
Behrens 2006(41)	Behrens P, Bitter T, Kurz B, and Russlies M. (2006) Matrix-associated autologous chondrocyte transplantation /implantation (MACT/MACI)-5-year follow-up. Knee 13:194-202
Genovese 2010(43)	Genovese E, Ronga M, Angeretti MG, Novario R, Leonardi A, Albrizio M, Callegari L, and Fugazzola C. (2010) Matrix-induced autologous chondrocyte implantation of the knee: mid-term and long-term follow-up by MR arthrography. Skeletal radiology 40:47-56
Ebert 2011(42)	Ebert JR, Robertson WB, Woodhouse J, Fallon M, Zheng MH, Ackland T, and Wood DJ. (2011) Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. The American journal of sports medicine 39:753-763
Ebert 2012(18)	Ebert JR, Fallon M, Zheng MH *et al.* (2012) A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weight bearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation : Findings at 5 Years. The American Journal of Sports Medicine; 40(7)
Marlovits 2012(44)	Marlovits S, Aldrian S, Wondrasch B, Zak L, Albrecht C, Welsch G, Trattnig S. (2012) Clinical and radiological outcomes 5 years after matrix-induced autologous chondrocyte implantation in patients with symptomatic, traumatic chondral defects. The American journal of sports medicine 40:2273-2280
Ventura 2012(45)	Ventura A, Memeo A, Borgo E, Terzaghi C, Legnani C, Albisetti W. Repair of osteochondral lesions in the knee by chondrocyte implantation using the MACI® technique (2012) Knee Surg Sports Traumatol Arthrosc. 20(1):121-6
Zak 2012(46)	Zak L; Aldrian S, Wondrasch B (2012) Ability to Return to Sports 5 Years After Matrix-Associated Autologous Chondrocyte Transplantation in an Average Population of Active Patients. The American Journal of Sports Medicine
Vijayan 2014(47)	Vijayan S, Bentley G, Rahman J et al. (2014) Revision cartilage cell transplantation for failed autologous chondrocyte transplantation in chronic osteochondral defects of the knee. Bone Joint Journal;96-B:54–8.
Nawaz 2014(48)	Nawaz SZ, Bentley G, Briggs T *et al.* (2014) Autologous Chondrocyte Implantation in the Knee J Bone Joint Surg Am; 96:824-830

Assessment of study methodology

A brief summary of key study characteristics for the included studies is presented in Table 33. The majority of studies were prospective case series or cohort studies with at least five years of follow-up for patients treated with MACI. Bartlett (2005)(35) was a prospective randomised trial comparing MACI and ACI. The results from the MACI arm have been presented here alongside observational data.

Table 33. Summary of the characteristics of included studies

Trial ID	Design characteristics	Compared interventions	Summary of main population characteristics	Main outcomes
Bartlett 2005(35)	Prospective randomised trial with 1 year follow-up	MACI and ACI	Patients 15 to 50 years with chondral defects sized ≥1	Modified Cincinnati Knee; Stanmore functional rating score; VAS
Behrens 2006(41)	Prospective case-series, 5 year follow-up	MACI	Patients aged 18 to 60 years with chondral defects sized 0.64 to 17.75 cm^2	Meyer; Tegner; Lysholm; ICRS; IKDC
Genovese 2010(58)	Prospective case-series, 5 year follow-up	MACI	Patients aged 20 to 50 years with chondral defects ≥ 2 cm^2	MRI (MOCART)
Ebert 2011(42)	Randomised trial (all MACI), 5 year follow-up	MACI	Patients aged 18 to 60 years with chondral defects sized 1.0 to 9.0 cm^2	KOOS; SF-36; MRI
Ebert 2012(59)	Randomised trial (all MACI), 5 year follow-up	MACI	Patients aged 16 to 63 years years with chondral defect sized 0.65 to 10.0 cm^2	MRI; KOOS; SF-36
Marlovits 2012(44)	Prospective case-series, 5 year follow-up	MACI	Patients aged 19 to 50 years with chondral defects sized >2 cm^2	KOOS; Modified Cincinnati Knee; Lysholm; IKDC
Ventura 2012(60)	Prospective case-series, 5 year follow-up	MACI	Patients aged 13 to 65 years with chondral defects sized 2.0 to 10.0 cm^2	VAS; Lysholm; Tegner MRI
Zak 2012(61)	Prospective case-series, 5 year follow-up	MACI	Patients aged 18-55 who met the German Societies of Traumatology and Orthopaedic Surgery regarding indications for ACI	KOOS; Noyes sports activity rating scale; Tegner score
Vijayan 2014(47)	Prospective cohort with 5 years follow-up	MACI or ACI	Patients 18-48 years with symptomatic isolated chondral or osteochondral lesion > 1 cm^2 in the knee	Cincinnati knee score; VAS
Nawaz 2014(48)	Retrospective cohort study with 10 years follow-up	MACI (n=519) or ACI	Patients aged 14-56 years with a symptomatic osteochondral defect range, 0.64 to 2.075 cm	Survival; VAS pain score; Stanmore functional rating score

Abbreviations: ACI, autologous chondrocyte implant; ICRS, international cartilage repair society; IKDC, international knee documentation committee; KOOS, knee injury and osteoarthritis outcome score; MACI, matrix-induced autologous chondrocyte implant; MRI, magnetic resonance imaging;RCT, randomised control trial; SF-36, 36-Item short-form health survey ; SRA, sports and recreational activities; VAS, visual analogue scale

Study participants – inclusion and exclusion criteria

A summary of the inclusion and exclusion criteria for the observational studies is provided in Table 34. The studies were comparable for age (range: 15 to 65 years) of included patients but varied in defect size included. The most common exclusion criterion was obesity (e.g. BMI>35).

Table 34. Inclusion and exclusion criteria for the observational studies

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Bartlett 2005(35)	Patients between 15 and 50 years of age, an isolated osteochondral defect larger than 1 cm^2 and the ability to follow the rehabilitation programme	Patients with osteoarthritis and inflammatory joint disease
Behrens 2006(41)	Patients between 18 and 60 with localized cartilage defects	Inflammable arthritis, total meniscectomy, knee instability, an inoperable valgus or varus deformity, patelladysplasia, or massive overweight (BMI>35)
Genovese 2010(58)	Grade III to IV lesions, according to the International Cartilage Repair Society scale (ICRS); Chondral or osteochondral lesions ≥2 cm of the femoral condyles, tibial plates, or patella in patients aged 18 to 50 years who had clinical symptoms such as knee pain or swelling	Arthritis or bipolar kissing lesions; Untreated knee instability or axial deviation; Infectious, tumoral, metabolic and inflammatory changes
Ebert 2011(42)	Treated with MACI; 15 to 65 years of age; deemed able to follow the rehabilitation program	A BMI >35, ligamentous instability, varus/valgusabnormalities; (>3º tibiofemoral anatomic angle); had undergone a prior extensive meniscectomy; or if they had ongoing progressive inflammatory arthritis
Ebert 2012(59)	Patients who had MACI; were 15 to 65 years of age and deemed able to follow the rehabilitation program	A BMI >35, ligamentous instability, varus/valgus abnormalities (>5 º tibiofemoral anatomic angle), had undergone a prior extensive meniscectomy, or had ongoing progressive inflammatory arthritis
Marlovits 2012(44)	Study participants were men and women 19 to 50 years of age with a defect size >2 cm^2 and no knee instability or malalignment (axis deviation >5 º)	Obese patients (>20% of normal body mass index); had a total or subtotal resected meniscus (but not after partial meniscectomy), severe neurological disorders, metabolic arthritis, joint infections, tumours, psychiatric diseases,

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		arthrofibrosis, or autoimmune diseases; or were pregnant
Ventura 2012(60)	Patients with symptomatic isolated or multiple localized osteochondral defects (2–10 cm^2)	Inflammable arthritis, osteonecrosis, osteoarthritis, patelladysplasia, prior total meniscectomy, an inoperable valgus or varus abnormality, and obesity (BMI>30)
Zak 2012(61)	Symptomatic traumatic defects of articular cartilage of the knee; no restriction in number of defects; defect size >2 cm^2; no knee instability; no malalignment; (axis deviation\5 └); female or male patients; age between 19 and 50 years	Patients younger than 50 years; patients with body mass index >20% over normal; patients with uncorrected axis deformity .5 └ ; patients who had total or subtotal meniscal resection; patients who were pregnant; and patients with severe neurologic disorders, metabolic arthritis, joint infection, tumor, psychiatric disease, arthrofibrosis, or autoimmune disease
Vijayan 2014(47)	A symptomatic isolated chondral or osteochondral lesion > 1 cm^2 in the knee, and were considered likely to be able to complete the rehabilitation programme. All patients had been treated with primary ACI or MACI, which had failed to heal, experiencing intolerable pain and knee swelling	A symptomatic isolated chondral or osteochondral lesion < 1cm^2 in the knee, could not complete rehabilitation
Nawaz 2014(48)	All skeletally mature patients with a symptomatic osteochondral defect, regardless of size or depth, that was confirmed with magnetic resonance imaging (MRI) or arthroscopy were offered chondrocyte implantation	Patients with tibiofemoral or patellar malalignment, clinical instability, a previous autologous chondrocyte implantation procedure, or known inflammatory arthritis were excluded from the study
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Study subjects - patient characteristics at baseline

A summary of patient characteristics from the observational studies is shown in

Table 35. Overall, the studies were comparable in age and gender, with mean defect size ranging between 3 and 6 cm^2.

Table 35. Baseline patient characteristics in the MACI observational studies

Characteristic	Barlett 2005	Behrens 2006	Genovese 2010	Ebert 2011	Ebert 2012 Accelerated rehabilitation	Ebert 2012 Traditional rehabilitation	Marlovits 2012	Ventura 2012	Zak 2012	Vijayan 2014	Nawaz 2014
N	47	38	13	41	31	32	21	53	70	22	519
Mean age, years	33.4	35	31	38.5	36.8	39.6	35.2	40	34.9	37.4	34
Sex (% male)	59	50	77	51	68	66	86	NR	73	55	63
BMI kg/m^2 Mean (SD)	NR	NR	NR	25.5	25.7	27.3	NR	NR (BMI >30 excluded)	NR	NR	NR
Defect size mean (SD)	6.0	4.1	4.2	3.0	3.21	3.32	5.1	4.3 (1.8)	5.3 (2.9)	4.47 **	4.09

Source: Bartlett 2005 p641; Behrens 2006 p195; Genovese 2010 p48; Ebert 2011 Table 1 p755; Ventura 2012 p122; Ebert 2012 p1528 and online supplement; Marlovitis 2012 Table 1 p2275; Zak 2012; Viajan 2014; Nawaz 2014
Abbreviations: BMI, body mass index; MACI, matrix-induced autologous chondrocyte implant; SD, standard deviation
** Converted to cm as defect sizes are reported in mm in the Vijayan paper.

Study outcomes

The outcomes assessed in the included studies are shown in

Table 36. The most commonly assessed outcome measures included KOOS pain and function, Tegner activity scale, Modified Cincinnati Knee Rating, MRI and the VAS.

Table 36. Outcomes assessed in the included observational studies

Outcome measure	Bartlett 2005(35)	Behrens 2006(41)	Genovese 2010(43)	Ebert 2011(42)	Ebert 2012(59)	Marlovits 2012(44)	Ventura 2012(45)	Zak 2012(46)	Vijayan 2014(47)	Nawaz 2014(48)
KOOS (including pain, function (SRA, ADL, QOL, other symptoms)	×	×	×	✓	✓	✓	×	✓	×	×
Tegner activity	×	✓	×	×	×	✓	✓	✓	×	×
Lysholm	×	✓	×	×	×	×	✓	×	×	×
ICRS score	×	✓	×	×	×	×	×	×	×	×
Stanmore functional rating score	✓	×	×	×	×	×	×	×	✓	✓
Modified Cincinnati Knee Rating	✓	×	×	×	×	✓	×	×	✓	✓
International Knee Documentation Committee Subjective Knee Evaluation	×	✓	×	×	×	✓	×	×	×	×
12-Item Short-Form Health	×	×	×	×	×	×	×	×	×	×

Outcome measure	Bartlett 2005(35)	Behrens 2006(41)	Genovese 2010(43)	Ebert 2011(42)	Ebert 2012(59)	Marlovits 2012(44)	Ventura 2012(45)	Zak 2012(46)	Vijayan 2014(47)	Nawaz 2014(48)
Survey										
Meyer	×	✓	×	×	×	×	×	×	×	×
SF 36	×	×	×	✓	✓	×	✓	×	×	×
EQ-5D	×	×	×	×	×	×	×	×	×	×
VAS	✓	×	✓	×	✓	×	✓	×	✓	✓
MRI	×	×	×	✓	✓	✓	✓	×	×	×

Statistical analysis

A description of the primary study hypothesis and statistical analyses are presented in Table 37.

Table 37. Study aim and statistical analyses

Trial no. (acronym)	Study aim/hypothesis	Statistical analysis
Bartlett 2005(35)	To compares the clinical, arthroscopic and histological outcomes of osteochondral defects in the knee treated by ACI-C or MACI in a randomised trial.	Clinical and arthroscopic assessments performed both pre-operatively and after one year were compared using paired and unpaired t-tests. The level of significance was set at $p < 0.05$.
Behrens 2006(41)	To clarify whether MACT proves suitable to treat cartilage defects and confirms objective and subjective clinical improvement over a period of up to 5 years after operation	Statistical tests were performed using the Wilcoxon test and the Kruskal–Wallis test.
Genovese 2010(43)	To define magnetic resonance arthrography imaging findings of MACI grafts of the knee in order to describe implant behaviour and to compare findings with validated clinical scores 30 and 60 months after MACI implant	NR
Ebert 2011(42)	A significant improvement in clinical and magnetic resonance imaging–based (MRI-based) outcomes after MACI will exist throughout the postoperative timeline to 5 years after surgery	To investigate the progression of clinical and MRI-based outcomes over time, a 1-way repeated measures analysis of variance was used. Dependent samples t tests were used to investigate differences in each dependent variable between the assessment time points
Ebert 2012(18)	A significant improvement will exist in clinical and magnetic resonance imaging (MRI)–based scoring measures to 5 years after surgery.	Repeated-measures analysis of variance (ANOVA) was used to investigate the progression of the clinical and MRI scores over the 5-year postoperative timeline between the accelerated and traditional groups.
Marlovits 2012(44)	A significant improvement in clinical and radiological outcomes after treatment of symptomatic, traumatic chondral defects of the knee with the MACI implant will be maintained up to 5 years after surgery.	For data analysis, a 1-way analysis of variance (ANOVA) with repeated measures was performed to compare the respective scores at the different time points, as the clinical outcome data approximately followed a normal distribution. Significance was reached at $P<.05$. Mean values and standard deviations were calculated for clinically meaningful changes in the KOOS, IKDC, modified Cincinnati, and Tegner-Lysholm scores.
Ventura 2012(45)	The study was carried out in order to evaluate clinical, radiographic, and histologic	Paired t test (two sided test and a = 0.05) was utilized to compare the preoperative and follow-up status.

Trial no. (acronym)	Study aim/hypothesis	Statistical analysis
	results with the MACI technique over a period of up to 5 years after operation.	Differences with a p value <0.05 were considered statistically significant.
Zak 2012(46)	At the time of midterm follow-up after matrix-associated autologous chondrocyte transplantation (MACT), return to recreational sports at the pre-injury level will be possible.	The Kruskal-Wallis test and the Bonferroni-Holm test were used to compare the different location-dependent groups pairwise, the Wilcoxon signed rank test for related variables to compute differences between pre- and postoperative clinical scores, and the Spearman rho correlation as a nonparametric test. A P value of <0.05 indicated statistically significant results
Vijayan 2014(47)	To report experience of revision cartilage transplantation performed in patients with chronically symptomatic articular cartilage lesions after failed ACI or MACI.	Mean pre- and post-operative scores were compared using the paired t-test. The level of statistical significance was set at a p-value < 0.05.
Nawaz 2014(48)	To evaluate the midterm to long-term functional outcomes of 827 patients treated with autologous chondrocyte implantation or MACI , retrospectively identifying factors that may have influenced the outcome. (Of the 827 patients 308 received ACI and 519 received MACI)	Univariate and multivariate analyses were undertaken to investigate the influence of specific factors on graft survival. Each factor was evaluated in separate Cox proportional hazards models with use of hazard ratios, with 95% CIs, describing the likelihood of failure when that particular factor was present. Wald tests were used to determine the significance of each variable.

Critical appraisal of study methodology

A summary of the quality assessment of included studies using a modified version of the STROBE checklist is provided in Appendix 7.

Key results of the observational studies

A summary of the key findings from each of the included studies is provided in Table 38. Overall, the results from these observational studies support the medium term efficacy of MACI.

Table 38. Summary of key findings from the observational and supportive studies

Study ID	Key results	Conclusion
Bartlett 2005(35)	Both MACI and ACI resulted in improvement of the clinical score after one year. The mean modified Cincinnati knee score increased by 17.6 in the ACI-C group and 19.6 in the MACI group (p = 0.32). Arthroscopic assessments performed after one year showed a good to excellent International Cartilage Repair Society score in 79.2% of ACI-C and 66.6% of MACI grafts. Hyaline-like cartilage or hyaline-like cartilage with fibrocartilage was found in the biopsies of 43.9% of the ACI-C and 36.4% of the MACI grafts after one year. The rate of hypertrophy of the graft was 9% (4 of 44) in the ACI-C group and 6% (3 of 47) in the MACI group. The frequency of re-operation was 9% in each group.	The clinical, arthroscopic and histological outcomes are comparable for both ACI-C and MACI. While MACI is technically attractive, further long-term studies are required before the technique is widely adopted.
Behrens 2006(41)	Five years after transplantation 8 out of 11 patients rated the function of their knee as much better or better than before. Three of the four scores (Meyer, Lysholm-Gilquist and ICRS) showed significant improvement compared to the preoperative value. One score, the Tegner–Lysholm score showed improvement, which, however, did not prove to be significant.	The significantly improved results on three scores after 5 years suggest that MACI represents a suitable but cost-intensive alternative in the treatment of local cartilage defects in the knee.
Genovese 2010(43)	At 60 months, the abnormality showed worsening in 1 out of 15 cases. Integration showed improvement in 3 out of 15 cases, and worsening in 3 out of 15 cases. Two surfaces of the implant showed further deterioration at 60 months, and 1 afflicted implant fully recovered after the same time interval. Implant contrast enhancement at 30 months was seen in 2 out of 15 cases, 1 of which recovered at 60 months. According to the MOCART score,	Magnetic resonance arthrography improved the evaluation of implants and facilitated the characterisation of MACI integration with contiguous tissues. The follow-up showed significant changes in MACI, even at 60 months, allowing for useful long-term MR evaluations.

Study ID	Key results	Conclusion
	4 cases were rated 68.4 out of 75 at 30 months and 65 out of 75 at 60 months. The mean clinical score decreased from 8.6 out of 10 at 30 months to 8.1 out of 10 at 60 months.	
Ebert 2011(42)	A significant improvement (P< .05) was demonstrated for all Knee injury and Osteoarthritis Outcome Score and SF-36 subscales over the postoperative timeline, as well as the 6-minute walk test and active knee extension. A significant improvement (P<.0001) was observed for the MRI composite score, as well as several individual graft scoring parameters. At 5 years after surgery, 67% of MACI grafts demonstrated complete infill, whereas 89% demonstrated good to excellent filling of the chondral defect. Patient demographics, cartilage defect parameters, and injury/surgery history demonstrated no significant pertinent correlations with clinical or MRI-based outcomes at 5 years, and no significant correlations existed between clinical and MRI-based outcome measures. At 5 years after surgery, 98% of patients were satisfied with the ability of MACI surgery to relieve knee pain; 86%, with improvement in their ability to perform normal daily tasks; and 73%, with their ability to participate in sport 5 years after MACI.	These results suggest that MACI provides a suitable midterm treatment option for articular cartilage defects in the knee. Long-term follow-up is essential to confirm whether the repair tissue has the durability required to maintain long-term patient quality of life. At 5 years after surgery, 98% of patients were satisfied with the ability of MACI surgery to relieve knee pain; 86%, with improvement in their ability to perform normal daily tasks; and 73%, with their ability to participate in sport 5 years after MACI.
Ebert 2012(59)	A significant time effect (P<.05) was demonstrated for all clinical and MRI-based scores over the 5-year period. While the VAS demonstrated significantly less frequent pain at 5 years in the accelerated group, there were no other significant differences between the 2 groups. Between 24 months and 5 years, a significant improvement (P<.05) in both groups was observed for	The outcomes of this randomized trial demonstrate a safe and effective accelerated rehabilitation protocol as well as a regimen that provides comparable, if not superior, clinical outcomes to patients throughout the postoperative timeline. At 5 years after surgery, 94% and 95% were satisfied with the ability of MACI to relieve their knee pain and

Study ID	Key results	Conclusion
	the sport and recreation subscale of the KOOS as well as a significant decrease (P<.05) in active knee extension for the traditional group. There were no significant differences (P< .05) in the MRI-based scores between 24 months and 5 years after surgery. Patient age and defect size exhibited significant negative correlations (P<.05) with several MRI-based outcomes at 5 years, while there were no significant correlations (P< .05) between clinical and MRI-based outcomes. At 5 years after surgery, 94% and 95% were satisfied with the ability of MACI to relieve their knee pain and improve their ability to undertake daily activities, respectively.	improve their ability to undertake daily activities, respectively.
Marlovits 2012(44)	Significant improvements (P<.05) were observed for all 5 KOOS subcategories at year 1 and were maintained through year 5 in 90.5%of patients (19/21). Treatment failure occurred in only 9.5%of patients (2/21). Significant improvements (P<.05) from baseline to year 5 were also observed for the IKDC score (30.1 to 74.3), the modified Cincinnati score (38.1 to 79.6), and the Tegner-Lysholm activity score (1.8 to 4.3). Similarly, the MOCART score significantly improved (P<.001) from baseline to year 5 (52.9 to 75.8). After 5 years, complete filling (83%) and integration (82%) of the graft were seen in the majority of patients. Signs of subchondral bone edema were still present in 47% of patients at 5 years. No product-specific adverse events were reported over the 5-year follow-up period.	Patients treated with a MACI implant demonstrated significant clinical improvement and good quality repair tissue 5 years after surgery. The MACI procedure was shown to be a safe and effective treatment for symptomatic, traumatic chondral knee defects in this study.
Ventura 2012(45)	Two years after transplantation, Lysholm score increased from a preoperative mean value of 70 (SD: 13.4) to 95 (SD: 6.4); the average VAS score decreased from a preoperative value of 5.2	The MACI technique is a safe and clinically effective procedure, which has been proven to be valuable in treating osteochondral defects even over the long term.

Study ID	Key results	Conclusion
	(SD: 2.9) to 1.9 (SD: 2.1). The difference with respect to Tegner activity level did not prove to be significant. At 1 year, MRI scans documented a completely repaired defect with slight sub-chondral bone abnormality in 38 cases (70%). Satisfying outcomes were confirmed on 17 patients who were re-evaluated 5 years after surgery. At 60 months, MRI scans showed complete integration with the surrounding native cartilage without any sign of detachment or bone marrow edema in 15 cases (88%).	
Zak 2012(46)	The results 5 years after MACT showed mean values of 60.1 for the KOOS–sport, 67.4 for the Noyes, and 3.8 for the Tegner scores, meaning that regular sports activity such as cycling or running on flat ground, as well as medium-level manual labour, is possible. It was noted that 74.3% of our patients returned to at least their pre-injury sports level.	Midterm postoperative results after MACT show that in a moderately active population, participation in regular sports is possible for most patients, at least at their pre-injury recreational level and intensity, and there is a good rate of return to sports.
Vijayan 2014(47)	The mean modified Cincinnati knee score improved from 40.5 (16 to 77) pre-operatively to 64.9 (8 to 94) at their most recent review ($p < 0.001$). The visual analogue pain score improved from 6.1 (3 to 9) to 4.7 (0 to 10) ($p = 0.042$). A total of 14 patients (63%) reported an 'excellent' (n = 6) or 'good' (n = 8) clinical outcome, 5 'fair' and one 'poor' outcome. Two patients underwent patellofemoral joint replacement.	This study demonstrates that revision cartilage transplantation with MACI after primary ACI and MACI can yield acceptable functional results and continue to preserve the joint.
Nawaz 2014(48)	Kaplan-Meier survival analysis revealed that the unadjusted graft survival rate was 78.2% at five years and 50.7% and ten years for the entire cohort. No difference was found between the survival rates of the ACI-C/ACI-P and MACI techniques (HR = 0.948, 95% CI = 0.738 to 1.219, $p = 0.678$). There was a significant postoperative	This study demonstrated an overall graft survival of 78% at five years and 51% beyond ten years following both autologous chondrocyte implantation techniques. Despite study limitations, the results demonstrate that autologous chondrocyte implantation/MACI for the treatment of osteochondral defects of the knee can achieve good results.

Study ID	Key results	Conclusion
	improvement in the function and pain scores of all three outcome measures ($p < 0.002$). Survivorship in the group with a previous cartilage regenerative procedure was inferior to that in patients with a previously untreated lesion, with failure five times more likely in the former group (HR = 4.718, standard error [SE] = 0.742, 95% CI = 3.466 to 6.420, $p < 0.001$). Degenerative change in any compartment had a significant detrimental effect on survivorship, with survivorship worsening as the osteoarthritis grade increased (Grade 1: HR = 2.077, 95% CI = 1.299 to 3.322, $p = 0.002$; Grade 2: HR = 3.450, 95% CI = 2.646 to 4.498, $p < 0.001$; and Grade 3: HR = 3.820, 95% CI = 2.185 to 6.677, $p < 0.001$).	

Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.8.2 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

SUMMIT

A summary of adverse events in the SUMMIT trial is shown in

n (%)	MACI (n=72)	Microfracture (n=72)
At Least 1 AE	57 (79.2)	61 (84.7)
At Least 1 TEAE	55 (76.4)	60 (83.3)
At Least 1 Related TEAE	25 (34.7)	28 (38.9)
At Least 1 Severe TEAE	7 (9.7)	10 (13.9)

At Least 1 SAE	11 (15.3)	19 (26.4)
At Least 1 TESAE	11 (15.3)	19 (26.4)
Discontinued Study Due to TEAE	1 (1.4)	1 (1.4)
Any Death	0	0

.**Error! Reference source not found.** The proportion of patients with at least 1 TEAE was 76.4% in the MACI implant group and 83.3% in the microfracture group. TESAEs were reported more frequently in the microfracture group (19 patients, 26.4%) than in the MACI implant group (11 patients, 15.3%). TEAEs considered related to study treatment and severe TEAEs occurred at comparable rates in the two treatment groups. One patient (1.4%) in each treatment group discontinued the study prematurely due to TEAEs. No patients died during the study.

Table 39. Summary of AEs (safety set [a])

n (%)	MACI (n=72)	Microfracture (n=72)
At Least 1 AE	57 (79.2)	61 (84.7)
At Least 1 TEAE	55 (76.4)	60 (83.3)
At Least 1 Related TEAE	25 (34.7)	28 (38.9)
At Least 1 Severe TEAE	7 (9.7)	10 (13.9)
At Least 1 SAE	11 (15.3)	19 (26.4)
At Least 1 TESAE	11 (15.3)	19 (26.4)
Discontinued Study Due to TEAE	1 (1.4)	1 (1.4)
Any Death	0	0

Source: SUMMIT Table 11-1 pg 118
Abbreviations: AE, adverse event; MACI, matrix-induced autologous chondrocyte implant; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event
[a] Includes all all randomised patients who underwent index arthroscopy

Common adverse events

An overview of TEAEs reported in >5% of patients in any treatment group, regardless of severity and relationship to study treatment, is provided in

n (%)	MACI (n=72)	Microfracture (n=72)
Any TEAE	55 (76.4)	60 (83.3)
Gastrointestinal Disorders	6 (8.3)	7 (9.7)
Abdominal pain	0 (0.0)	5 (6.9)
General Disorders and Administration Site Conditions	10 (13.9)	10 (13.9)
Pyrexia	4 (5.6)	2 (2.8)
Treatment failure	1 (1.4)	4 (5.6)
Infections and Infestations	23 (31.9)	17 (23.6)
Influenza	4 (5.6)	5 (6.9)
Nasopharyngitis	10 (13.9)	7 (9.7)
Injury, Poisoning and Procedural Complications	19 (26.4)	20 (27.8)
Cartilage injury	3 (4.2)	9 (12.5)
Procedural pain	3 (4.2)	4 (5.6)
Musculoskeletal and Connective Tissue Disorders	48 (66.7)	52 (72.2)
Arthralgia	37 (51.4)	46 (63.9)
Back pain	8 (11.1)	7 (9.7)
Joint effusion	5 (6.9)	4 (5.6)
Joint swelling	7 (9.7)	4 (5.6)
Ligament sprain	2 (2.8)	4 (5.6)
Nervous System Disorders	16 (22.2)	24 (33.3)
Headache	13 (18.1)	21 (29.2)
Respiratory, Thoracic and Mediastinal Disorders	5 (6.9)	5 (6.9)

. The most commonly reported individual TEAEs were nasopharyngitis (13.9% in the MACI implant group versus 9.7% in the microfracture group), cartilage injury (4.2% versus 12.5%), arthralgia (51.4% versus 63.9%), back pain (11.1% versus 9.7%) and headache (18.1% versus 29.2%).

Table 40. TEAE per system organ class reported in >5% of patients in any treatment group (safety set [a])

n (%)	MACI (n=72)	Microfracture

		(n=72)
Any TEAE	55 (76.4)	60 (83.3)
Gastrointestinal Disorders	6 (8.3)	7 (9.7)
Abdominal pain	0 (0.0)	5 (6.9)
General Disorders and Administration Site Conditions	10 (13.9)	10 (13.9)
Pyrexia	4 (5.6)	2 (2.8)
Treatment failure	1 (1.4)	4 (5.6)
Infections and Infestations	23 (31.9)	17 (23.6)
Influenza	4 (5.6)	5 (6.9)
Nasopharyngitis	10 (13.9)	7 (9.7)
Injury, Poisoning and Procedural Complications	19 (26.4)	20 (27.8)
Cartilage injury	3 (4.2)	9 (12.5)
Procedural pain	3 (4.2)	4 (5.6)
Musculoskeletal and Connective Tissue Disorders	48 (66.7)	52 (72.2)
Arthralgia	37 (51.4)	46 (63.9)
Back pain	8 (11.1)	7 (9.7)
Joint effusion	5 (6.9)	4 (5.6)
Joint swelling	7 (9.7)	4 (5.6)
Ligament sprain	2 (2.8)	4 (5.6)
Nervous System Disorders	16 (22.2)	24 (33.3)
Headache	13 (18.1)	21 (29.2)
Respiratory, Thoracic and Mediastinal Disorders	5 (6.9)	5 (6.9)

Source: SUMMIT Table 11-2 pg 119-120
Abbreviations: MACI, matrix-induced autologous chondrocyte implant TEAE, treatment-emergent adverse event
[a] Includes all all randomised patients who underwent index arthroscopy

Discontinuations due to adverse events

One patient (1.4%) in each treatment group discontinued the study prematurely due to treatment-emergent AEs. The patient from the MACI implant group discontinued due to impaired healing of the target knee that was moderate in intensity and possibly related to study treatment. The patient in the microfracture group discontinued due traumatic fracture and head

injury; both of which were severe in intensity and not related to study treatment.

Serious adverse events

An overview of TESAEs, regardless of severity and relationship to study treatment, is presented in Table 41. TESAEs were reported more frequently in the microfracture group (26.4%) than in the MACI implant group (15.3%). The difference in incidence rates was mainly due to more serious cases of treatment failure, cartilage injury, and arthralgia in the microfracture group compared with the MACI implant group.

TESAEs reported in more than 1 patient within any treatment group were treatment failure (1 patient in the MACI implant group and 4 patients in the microfracture group), cartilage injury (2 patients in the MACI implant group and 6 patients in the microfracture group), meniscus lesion (2 patients in the MACI implant group only), and arthralgia (3 patients in the microfracture group only).

Table 41. Summary of TESAEs (safety set [a])

n (%)	MACI (n=72)	Microfracture (n=72)
Any TESAE	11 (15.3)	19 (26.4)
Cardiac Disorders	1 (1.4)	0 (0.0)
Arrhythmia	1 (1.4)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	1 (1.4)
Abdominal pain	0 (0.0)	1 (1.4)
General Disorders and Administration Site Conditions	2 (2.8)	4 (5.6)
Impaired healing	1 (1.4)	1 (1.4)
Treatment failure	1 (1.4)	4 (5.6)
Infections and Infestations	1 (1.4)	1 (1.4)
Pneumonia	1 (1.4)	0 (0.0)
Post-operative wound infection	0 (0.0)	1 (1.4)
Wound infection staphylococcal	0 (0.0)	1 (1.4)
Injury, Poisoning and Procedural Complications	5 (6.9)	7 (9.7)
Cartilage injury	2 (2.8)	6 (8.3)
Graft delamination	1 (1.4)	0 (0.0)
Head injury	0 (0.0)	1 (1.4)
Meniscus lesion	2 (2.8)	0 (0.0)
Transplant failure	1 (1.4)	0 (0.0)
Traumatic fracture	0 (0.0)	1 (1.4)
Musculoskeletal and Connective Tissue Disorders	1 (1.4)	7 (9.7)
Arthralgia	0 (0.0)	3 (4.2)
Arthritis	0 (0.0)	1 (1.4)
Joint lock	0 (0.0)	1 (1.4)
Knee deformity	1 (1.4)	0 (0.0)
Loose body in joint	0 (0.0)	1 (1.4)
Osteochondrosis	0 (0.0)	1 (1.4)
Pain in extremity	0 (0.0)	1 (1.4)
Patellofemoral pain syndrome	0 (0.0)	1 (1.4)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (1.4)	0 (0.0)
Prostate cancer	1 (1.4)	0 (0.0)

Nervous System Disorders	0 (0.0)	1 (1.4)
Multiple sclerosis	0 (0.0)	1 (1.4)
Pregnancy, Puerperium and Perinatal Conditions	1 (1.4)	1 (1.4)
Abortion spontaneous	1 (1.4)	1 (1.4)
Renal and Urinary Disorders	1 (1.4)	0 (0.0)
Urinary retention	1 (1.4)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	1 (1.4)	1 (1.4)
Pulmonary embolism	1 (1.4)	1 (1.4)
Vascular Disorders	1 (1.4)	0 (0.0)
Thrombosis	1 (1.4)	0 (0.0)

Source: SUMMIT Table 11-5 pg 123-124
Abbreviations: MACI, matrix-induced autologous chondrocyte implant; TESAE, treatment-emergent serious adverse event
[a] Includes all all randomised patients who underwent index arthroscopy

No deaths occurred in the study.

SUMMIT extension

Overall, the interim safety results in this extension study are consistent with that reported in the MACI00206 clinical study report (results through Week 104). No safety concerns have been observed and the safety profile remains consistent with the known safety profile of MACI.

AE

The proportion of patients with at least one AE of interest within three years was 11.1% in the MACI group and 4.2% in the microfracture group. Consistent with the results of the MACI00206 study, haemarthrosis was the only AE of interest reported in more than 1 patient in any treatment group (2 patients [2.8%] in the MACI group and 1 patient [1.4%] in the microfracture group).

TEAE

The proportion of patients with at least 1 TEAE within three years was 79.2% in the MACI group and 86.1% in the microfracture group. The overall incidence of TEAEs did not increase at Year 3 (MACI: 50.0%, microfracture: 39.3%) compared to that at Year 1 (MACI: 69.4%, microfracture: 73.6%) and Year 2 (MACI: 55.6%, microfracture: 60.6%). The incidence of TEAEs

considered related to study treatment within three years was comparable between the two treatment groups at Week 156 (27 patients [37.5%] in the MACI group and 30 patients [41.7%] in the microfracture group). This result is similar to that seen within two years (MACI: 25 patients [34.7%], microfracture: 28 patients [38.9%]). No patients have discontinued this extension study prematurely due to TEAEs or other reasons (prior to Week 104, one patient in each treatment group discontinued the study due to a TEAE).

TESAE

The incidence of TESAEs within three years was comparable between the treatment groups: MACI=26.4%, microfracture=31.9%. The incidence of TESAEs within two years slightly favoured the MACI group: MACI=15.3%, microfracture=26.4%. Within three years, there were no TESAEs reported for 5% or more of patients in the MACI treatment group, but there were three TESAEs reported for 5% or more of patients in the microfracture group: arthralgia (5 patients [6.9%]), treatment failure (6 patients [8.3%]), and cartilage injury (7 patients [9.7%]).

No deaths occurred in this study.

Basad (2010)(36)

There were no treatment-related safety issues during the study. Any irritation experienced on increased weight bearing was eased by treatment with non-steroidal anti-inflammatory drugs and returning to partial weight-bearing for an additional week. One patient in the MACITM group had persistent pain after 12 months. A second-look arthroscopy showed an even and firm regenerated tissue surface with good bonding to the surrounding tissue.

5.8.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Safety analyses for SUMMIT show that MACI implant and microfracture have comparable safety profiles. TESAEs were reported more frequently in the microfracture group (19 patients, 26.4%) than in the MACI implant group (11 patients, 15.3%).

5.9 *Interpretation of clinical evidence*

5.9.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

In the SUMMIT trial, treatment with MACI implant resulted in a significantly greater increase in KOOS Pain and Function scores from the baseline level compared with microfracture (p=0.001). The difference in mean change in pain score from baseline to 104 Weeks was 11.76 and the mean change in function (SRA) score was 11.41. MACI implant was also superior to microfracture for response rate based on KOOS scores and change in other KOOS domain scores.

[redacted]

In the Basad (2010)(36) study, MACI was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm (P = 0.005), Tegner (P = 0.04), ICRS patient (P = 0.03) and ICRS surgeon (P = 0.02) scores. There were no safety issues related to MACI or MF during the study. Therefore MACI was considered superior to MF in the treatment of articular defects over 2 years.

5.9.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The pivotal comparative evidence for MACI is derived from one well conducted, multiple-centre, RCT, conducted over two years, with medium terms data from a three year open-label extension, and one single centre two-year RCT. As with many surgical studies, blinding of investigators and participants is almost impossible. However, in the SUMMIT study, outcome assessors were blinded to treatment allocation ensuring that measurement bias was avoided.

The fact that the trial included a large number of centres also meant that there has been no surgeon selection, ie only good surgeons were selected for MACI versus MF. The data has shown that results are consistent between centres indicating an absence of bias.

The evidence provided includes longer-term (3-year) data providing some of the much-needed evidence base that MACI implants are effective over the longer term which to date was not available.

A relevant and much used comparator has been used in the SUMMIT trial which makes any results relevant and well interpretable.

Furthermore the trial included a range of lesion sizes. This allowed MACI and MF to be evaluated in a relatively wide range of patients. The evidence is therefore also more relevant to clinical practice, where a wide range of lesions will be seen and treated.

Furthermore, the SUMMIT trial (and extension) represent the largest RCT in cartilage repair to date, comparing MACI to MF, a relevant comparator

Finally the SUMMIT trial included a large range of clinical outcome measures in addition to the KOOS such as MRI assessment, histological assessment, the Modified Cincinnati Knee Rating System and the International Knee Documentation, which provided additional proof of the benefits of MACI versus MF. In addition quality of life measures were included, providing additional but different insights.

Though we have presented 3 year data in this submission, these only represent relatively short-term results and longer term data are needed. This is evidenced by the fact that the extension study has a 3-year duration. However, 2 and 3 year results are in line with efficacy at similar time points in single centre cohort studies such as the study by Ebert.(42)

Histological assessment is complex as the results can vary in the same patients between samples taken at different sites. Also the interpretation of results is challenging even for very experienced assessors. Therefore histological data cannot alone, be provide persuasive evidence, which is why histological findings were only included as a secondary outcome in the SUMMIT trial.

The SUMMIT trial used the 4-phase standardized rehabilitation programme as described by Steadman(62) and this was the same for both MACI and MF patients. Compliance with the rehabilitation programme was high and may have improved the results in both arms. It is conceivable that this benefitted the MF arm as results for this technique were better in the SUMMIT trial than in other RTCs, cohort studies or real life.(7)

A final limitation of the SUMMIT study is that surgeons were only able to contribute a small number of patients. However, as with any surgical procedure, the more frequently the surgeon performs it, the better the outcome of these surgeries. Therefore it is possible that less experienced surgeons provided suboptimal outcomes of interventions, though this can have affected both treatment arms.

5.9.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

This submission includes long-term data on MACI and MF and clearly shows that treatment with MACI leads to better results than with MF in lesions between 3 and 20cm2. However, it should be noted that MF is not normally used in lesions larger than 12-13 cm2.(62)

An indirect comparison, though from 2013, is available and shows that treatment with MACI is not significantly different from ACI but better than MF. This is in line with current long-term clinical results.

From the clinical data is clear that efficacy of MACI is independent of lesion size. This indicates that MACI can also be used as an alternative to mosaicplasty even if the actual indications of MACI is not for lesions less than 3 cm2. Data from Solheim(63) and Bentley(30) well as the indirect comparison show that mosaicplasty is less effective than MACI and MF.

Furthermore, data from Gomoll further shows that MACI also produces very good results in the patella, in addition to the femoral chondyle and thus should also be considered for use for lesions in the patella. This is shown by long-term (4yr) data on 110 patients, 86% of whom rated their knees as good or

excellent after an ACI intervention(64). These results are echoed by those published by Briant.(65)

5.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Patients receiving MACI implants are those younger patients who have mostly had an acute traumatic or sports injury. The patient population included in the clinical trial data reflects these patients very well, aiming at patients between 18 years and 55 years of age. Therefore we are of the opinion that the trial data is comparable to the real world population. In clinical practice, eligibility for MACI would be assessed using selection criteria very similar to those used for the SUMMIT trial ie age (between 18 and 55 years of age), post-traumatic, single, isolated, symptomatic chondral defects (4–10 cm^2) of the femoral condyle etc.

Furthermore the SUMMIT trial included patients from 14 centres in 7 countries, and thus also provides a good representation of patients everywhere not just in England and Wales. The study represents the largest RCT in cartilage repair to date, comparing different treatment modalities, and thus provides valid results.

As MACI is not a regular drug, the dose was arrived at empirically and there is no real evidence base, other than the clinical trial data.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Due to the acquisition of MACI by Aastrom from Sanofi, it was not possible to carry out a cost-effectiveness analysis. Cost-effectiveness evidence was presented to the MSAC submission in January 2013 and it was the aim to adapt this model to the English and Welsh situation, however due to time constraints in terms of the submission timelines, this was not possible. Therefore, there is no economic evidence available for MACI for England and Wales.

The Australian cost-effectiveness model, which was based on the SUMMIT trial concluded that MACI was cost-effective. The submission in Australia focussed on lesion sizes between 2-4 cm^2. However MACI was not listed in Australia due to a purported lack of evidence on the short-term and long-term benefits of (M)ACI versus MF and mosaicplasty though the MSAC did agree in their report(66) that " that MACI and/or ACI may potentially be more effective for patients with large chondral lesions (>2cm^2), however this was not supported by high quality evidence". However this evidence is now available. In addition the target group is lesion sizes between 3 and 20 cm^2 which is more appropriate given that evidence has shown that efficacy of MACI is not limited by lesion size.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Table 42 Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Study 1							
Study 2							
Etc.							
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Response

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Response

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

Response

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Response

6.2.4 Please define what the health states in the model are meant to capture.

Response

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Response

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 43 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon			
Cycle length			
Half-cycle correction			
Were health effects measured in QALYs; if not, what was used?			
Discount of 3.5% for utilities and costs			
Perspective (NHS/PSS)			
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Response

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).

- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Response

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Response

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Response

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has

not been included, provide an explanation of why it has been excluded.

Response

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Response

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Response

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 44 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	A years	x to y (normal)	Patient characteristics section 6.3.4
Overall survival	B months	x to y (Weibull)	Trial results section 6.5
Etc.	…	…	…
CI, confidence interval			

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Response

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Response

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Response

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Response

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Response

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Response

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.

- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Response

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Response

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Response

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 45 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Health state 1	HS1			
Health state 2	HS2			
Etc.	…		…	
Adverse event 1	AE1			
Adverse event 2	AE2			

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Response

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Response

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Response

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Response

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Response

6.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Response

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Response

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Response

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study

- costs for use in economic analysis
- technology costs.

Response

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Response

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 46 Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Ref. in submission	Comparator 1 (confidence interval)	Ref. in submission	Etc.
Technology cost					
Mean cost of technology treatment					
Administration cost					
Monitoring cost					
Tests					
Etc.	…		…		…
Total					

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table 47 List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Health state 1	Technology		
	Staff		
	Hospital costs		
	Etc.		
	Total		
Health state 2			
Etc.	…	…	…

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Table 48 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
Adverse event 1	Technology		
	Staff		
	Hospital costs		
	Etc.		
	Total		
Adverse event 2	Technology		
	Staff		
Etc.	…	…	…

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Response

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Response

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Response

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Response

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 49 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Progression-free survival	C_1	R_1
Post-progression survival	C_2	R_2
Overall survival	C_{1+2}	R_{1+2}
Adverse event 1	C_3…	$R_{3...}$
Etc.	…	…

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Response

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Response

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 50 Model outputs by clinical outcomes

Outcome	LY	QALY	Cost (£)
Progression-free survival	L_1	$QALY_1$	$Cost_1$
Post-progression survival	L_2	$QALY_2$	$Cost_2$
Overall survival	L_{1+2}	$QALY_{1+2}$	$Cost_{1+2}$
Adverse event 1	L_3	$QALY_3$	$Cost_3$
Etc.	…	…	…
LY, life years; QALY, quality-adjusted life year			

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 51 Summary of QALY gain by health state

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Health state 1 (HS1)	X_{HS1}	Y_{HS1}	$X_{HS1} – Y_{HS1}$	$\|X_{HS1} – Y_{HS1}\|$	$\|X_{HS1} – Y_{HS1}\|$/ (Total absolute increment)
HS2	X_{HS2}	Y_{HS2}	$X_{HS2} – Y_{HS2}$	$\|X_{HS2} – Y_{HS2}\|$	$\|X_{HS2} – Y_{HS2}\|$/ (Total absolute increment)
…	…	…	…	…	…
Adverse event 1 (AE1)	X_{AE1}	Y_{AE1}	$X_{AE1} – Y_{AE1}$	$\|X_{AE1} – Y_{AE1}\|$	$\|X_{AE1} – Y_{AE1}\|$/ (Total absolute increment)
AE2	X_{AE2}	Y_{AE2}	$X_{AE2} – Y_{AE2}$	$\|X_{AE2} – Y_{AE2}\|$	$\|X_{AE2} – Y_{AE2}\|$/ (Total absolute increment)
Total	X_{Total}	Y_{Total}	$X_{Total} – Y_{Total}$	Total absolute increment	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 52 Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Health state 1 (HS1)	X_{HS1}	Y_{HS1}	$X_{HS1} – Y_{HS1}$	$\|X_{HS1} – Y_{HS1}\|$	$\|X_{HS1} – Y_{HS1}\|$/ (Total absolute increment)
HS2	X_{HS2}	Y_{HS2}	$X_{HS2} – Y_{HS2}$	$\|X_{HS2} – Y_{HS2}\|$	$\|X_{HS2} – Y_{HS2}\|$/ (Total absolute increment)
…	…	…		…	…
Adverse event 1 (AE1)	X_{AE1}	Y_{AE1}	$X_{AE1} – Y_{AE1}$	$\|X_{AE1} – Y_{AE1}\|$	$\|X_{AE1} – Y_{AE1}\|$/ (Total absolute increment)
AE2	X_{AE2}	Y_{AE2}	$X_{AE2} – Y_{AE2}$	$\|X_{AE2} – Y_{AE2}\|$	$\|X_{AE2} – Y_{AE2}\|$/ (Total absolute increment)
Total	X_{Total}	Y_{Total}	$X_{Total} – Y_{Total}$	Total absolute increment	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 53 Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Technology cost	X_{tech}	Y_{tech}	$X_{tech} – Y_{tech}$	$\|X_{tech} – Y_{tech}\|$	$\|X_{tech} – Y_{tech}\|$/ (Total absolute increment)
Mean total treatment cost	X_{treat}	Y_{treat}	$X_{treat} – Y_{treat}$	$\|X_{treat} – Y_{treat}\|$	$\|X_{treat} – Y_{treat}\|$/ (Total absolute increment)
Administration cost	X_{admin}	Y_{admin}	$X_{admin} – Y_{admin}$	$\|X_{admin} – Y_{admin}\|$	$\|X_{admin} – Y_{admin}\|$/ (Total absolute increment)
Monitoring cost	X_{mon}	Y_{mon}	$X_{mon} – Y_{mon}$	$\|X_{mon} – Y_{mon}\|$	$\|X_{mon} – Y_{mon}\|$/ (Total absolute increment)
Tests	X_{tests}	Y_{tests}	$X_{tests} – Y_{tests}$	$\|X_{tests} – Y_{tests}\|$	$\|X_{tests} – Y_{tests}\|$/ (Total absolute increment)
Etc.	…	…	…	…	…
Total	X_{Total}	Y_{Total}	$X_{Total} – Y_{Total}$	Total absolute increment	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits					

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 54 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Response

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Response

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Response

6.7.10 What were the main findings of each of the sensitivity analyses?

Response

6.7.11 What are the key drivers of the cost-effectiveness results?

Response

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Response

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Response

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Response

6.9.3 Please describe how the statistical analysis was undertaken.

Response

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Response

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Response

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Response

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Response

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Response

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Response

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Aastrom expect that up to 500 individuals are eligible for treatment with MACI. This maximum of 500 is expected at year 5. This is based on the estimate that was provided by NICE in the scope of the current technology assessment. It is expected that the total number of cartilage procedures will increase with the number of knee arthroscopies performed, which keeps pace with population growth. This is expected to be 0.6% per year between 2010 and 2035, and this was used to estimate the total number of cartilage procedures in year 1 to 5 (Table 55). We have included only MF and MACI/ACI as we were limiting ourselves to lesion sizes between 3-20cm2 for which mosaicplasty is not indicated.

Table 55 Procedure numbers by year

Product	Year 1	Year 2	Year 3	Year 4	Year 5
MACI	175	180	200	225	250
ChondroCelect	175	180	200	225	250
MF	9,256	9,304	9,322	9,330	9,339

Total	9,606	9,664	9,722	9,780	9,839

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

We have assumed the maximum number of procedures as estimated by NICE will be carried out in year 5 and that the 500 patients are divided equally between MACI and ChondoCelect.. The remainder of procedures would be carried out using MF. We have also assumed that patients will get one procedure, with the exception of re-opeations, which have been included separately.

7.3 What assumption(s) were made about market share (when relevant)?

We have assumed that the 500 patients/procedures are divided equally between MACI and ChondoCelect. this is based on the expected mean lesion size being in the range 4 to 7 cm^2 . We have assumed that no other treatments have any market share in this market which was defined as cartilage lesions with a size between 3 and 20 cm^2.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the costs that we have included, it is reasonable to assume that the re-operations after MF, even with MACI or ACI, do not have the same success rates as primary MACIs or ACIs. This is based on long-term data from the longitudinal follow up of patients which indicated an 80% success rate of MACI after a patient had first been treated with MF and then re-treated with MACI or ACI, as evidence by several studies. [Minas 2009] [Nawaz 2014] [Vijayan 2014] This would then lead to additional costs downstream which currently have not been included in the budget impact model.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for MACI and ACI are list prices, obtained from Aastrom and eMC dictionary of medicines and devices respectively. Cost for MF is based on NHS reference costs. Cost for the procedure used to implant either ACI or MACI has been assumed to have the same costs as MF. This cost was obtained from NHS reference costs, elected procedures 2013.

7.6 Were there any estimates of resource savings? If so, what were they?

There are resource savings from using MACI (or ACI) as a first-line treatment option, based on the long-term success rate of MACI, which is higher than that of MF[redacted], based on the SUMMIT study and 1 year extension data. However, data from the Saris 2009(57) study comparing ACI to MF reported failure rates of 2.9% and 11.5% respectively. It is widely believed that the MF failure rate observed in the SUMMIT trial is much lower than in clinical practice (possibly due to the study-determined rehabilitation programme), and therefore we thought it of importance to include an additional analysis that uses other published rates. Using these will lead to more treatment failures with MF than in the base cases analysis, which will require additional interventions. Based on clinical opinion, we have assumed that all failures with MACI or ChondroCelect will result in a repeat MACI/ACI, while all failed MFs will result in a MACI or ACI. The changed failure rates of these re-operations have not been taken into account in this model but should again offer additional savings as repeat MACI/ACI have higher success rates after a prior MACI/ACI (9% failure rate)(47) than after a prior MF (~20% failure rate).(67)

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for England and Wales is as shown in Table 56 below. This includes both MACI and ACI. The budgetary impact model demonstrates that in year 1, the impact of MACI/ACI amounts to £3.7m rising to £8.3m in year 5. This amounts to £16,689 per implant (based on 500 original implants), i.e. lower than the cost of the implantation (an average of £17,263 for MACI and ACI) and rehab, showing that there are cost-offsets versus MF alone as a first-line treatment.

Table 56 Budgetary impact MACI and ACI

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
World with MACI and ChondroCelect 1st line	**36,558,890**	**39,580,284**	**43,101,444**	**44,173,026**	**45,226,498**
World without	**30,577,328**	**33,486,579**	**36,416,996**	**36,646,628**	**36,877,274**
Difference = budgetary impact	**5,981,562**	**6,093,704**	**6,684,448**	**7,526,398**	**8,349,223**

However using the alternative failure rates as obtained from the Saris 2009(57) study we performed an additional analysis which takes into account the higher failure rates for both ACI/MACI and MF. This results in more re-operations for MF and thus reduces the overall budget impact model to around £7.8m in year 5, equating to around £15,569 per implantation (based on 500 original implants), indicating the further savings from the higher failure rate of MF as shown in Table 57 below.

Table 57 Budgetary impact MACI/ACI using Saris failure rates

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
World with MACI and ChondroCelect 1st line	**41,418,086**	**49,318,839**	**57,758,646**	**58,851,428**	**59,925,062**
World without	**35,577,663**	**43,527,574**	**51,518,813**	**51,829,096**	**52,140,393**
Difference = budgetary impact	**5,840,424**	**5,791,265**	**6,239,833**	**7,022,332**	**7,784,669**

The calculations related to the re-operations may include a slight overestimation as these did not take into account the re-operations already having occurred.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not included as part of the budgetary impact, are potential cost savings due to a reduction in the loss of work productivity. This is especially relevant to this group of patients who are relatively young and likely to be employed.

8 References

Please use a recognised referencing style, such as Harvard or Vancouver.

Response

9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

9.2.2 The date on which the search was conducted.

Response

9.2.3 The date span of the search.

Response

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Response

9.2.6 The inclusion and exclusion criteria.

Response

9.2.7 The data abstraction strategy.

Response

9.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

SUMMIT		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	An Interactive Voice Response System was used	Yes
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Comparable baseline demographic and disease characteristics	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)?	Outcome assessors were blinded but participants and care providers were not	Outcome Assessors: Yes Care Providers: No Participants: No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?		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?	All randomized and treated patients were analyzed. Last observation carried forward was used for missing data imputation	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Basad (2010)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Patients were allocated consecutive numbers in the order of their study entry and then randomised to receive either MACI or MF via a computer-generated randomisation list	Yes
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes, except for the difference in symptom duration, which was 0.3 years longer in the MF group	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 blinding was reported. Not blinding outcome assessors could have introduced bias into outcome assessment tools	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The MF group had three dropouts. One patient became pregnant 6 months after treatment, one was an early treatment failure and received OATS after 10 months, and one discontinued without giving a reason. One patient discontinued from the MACI group without stating a reason	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NA	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?	All available data (not just those from patients with complete records) were used as this analysis is able to deal with incomplete records as long as missing values could be considered ‘‘missing completely at random’’, which was the case	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD’s guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
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)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

Summary of search strategies

Database (dates covered)	**Search terms**	**Citations retrieved**	**Final number of citations (excluding duplicate citations)**
EMBASE.com (Includes MEDLINE and EMBASE 1966	#1: 'knee'/exp OR 'knee injury'/exp OR 'knee injury'/syn OR knee* OR patella* OR trochlea* OR (lateral OR medial OR femoral OR femur OR tibial AND condyle*) OR 'distal femur'	151,078	605

Database (dates covered)	Search terms	Citations retrieved	Final number of citations (excluding duplicate citations)
to August 2012) (*Searched on 21 August 2012*)	#2: cartilag*:de,ab,ti OR chondrocyt*:de,ab,ti OR osteochondral*:de,ab,ti OR chondral*:de,ab,ti OR 'chondrogenesis'/exp OR 'cartilage cell'/exp OR 'cartilage cell'/syn OR 'or articular cartilage' OR 'cartilage injury'/exp OR 'cartilage degeneration'/exp OR 'osteochondritis dissecans'/exp OR 'osteochondritis dissecans'/syn	105,061	
	#3: 'autotransplantation'/syn OR 'autotransplantation'/exp OR (autolog* OR autogen* OR chondrocyt* AND (transplant* OR implant*)) OR maci OR aci OR chondrocelect OR tgx001 OR cartipatch OR biocart	81,224	
	#4: 'chondroplasty'/exp OR chondroplasty OR 'microfracture'/exp OR microfracture OR 'micro fracture' OR 'marrow stimulating technique' OR 'articular drilling' OR 'articular resurfacing'	1,272	
	#5: mosaicplasty OR 'mosaic chondroplasty' OR (osteochondral OR chondral OR cartilag* AND (autograft* OR allograft* OR graft*))	10,551	
	#6: #3 OR #4 OR #5	89,321	
	#7: #1 AND #2 AND #5	3,102	

Database (dates covered)	Search terms	Citations retrieved	Final number of citations (excluding duplicate citations)
	#8: 'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,598,769	
	#9: #7 AND #8	606	
Cochrane library (*searched 21 August 2012*) • Cochrane reviews • Other reviews • Technology assessments • Trials	#1: "knee"/exp OR knee* OR patella* OR trochlea* OR (lateral OR medial OR femoral OR femur OR tibial AND condyle*) OR "distal femur"	19,943	151
	#2: cartilag* OR chondrocyt* OR osteochondral* OR chondral* OR "chondrogenesis"/exp OR "cartilage"/exp OR "cartilage diseases"/exp OR "cartilage, articular"/exp OR "osteochondritis dissecans"/exp OR "osteochondritis dissecans"	1,071	
	#3: "transplantation, autologous"/exp OR (autolog* OR autogen* OR chondrocyt* AND (transplant* OR implant*)) OR maci OR chondrocelect OR tgx001 OR cartipatch OR biocart	5,287	
	#4: "arthroplasty, subchondral"/exp OR microfracture OR "micro fracture" OR "marrow stimulating technique" OR "articular drilling" OR "articular resurfacing"	33	
	#5: mosaicplasty OR "mosaic chondroplasty" OR (osteochondral OR chondral OR cartilag* AND (autograft* OR allograft* OR graft*))	154	
	#6: #3 OR #4 OR #5	5,380	

Database (dates covered)	Search terms	Citations retrieved	Final number of citations (excluding duplicate citations)
	#7: #1 AND #2 AND #6	151	

9.4.1 Inclusion and exclusion criteria.

Table 58. Summary of the selection process for included studies

Total number of studies identified for full text review	**14**
Number of citations excluded after full text review	
• Trial does not contain a KOOS responder analysis (MACI, ACI and microfracture studies)	7
• Trial does not contain the Modified Cincinnati Knee (mosaicplasty studies only)	4
• Trial duration was not comparable to SUMMIT trial (2 years)	1
Total number of citations excluded	12
Total number of included studies	**2**

Abbreviations: ACI, autologous chondrocyte implant; KOOS, knee injury and osteoarthritis outcome score; MACI, matrix-induced autologous chondrocyte implant

9.4.2 The date on which the search was conducted.

- a search of published literature using the electronic database EMBASE.com, which allows concurrent searching of EMBASE and MEDLINE (conducted on 26 June 2012)
- a search of the Cochrane Library and other health technology assessment (HTA) websites (conducted between 26 to 29 June 2012)
- grey literature search (conducted between 26 to 29 June 2012)
- manual checking of reference lists of all relevant articles. (conducted between 26 to 29 June 2012)

9.4.3 The date span of the search.

1996 to November 2012

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See above

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Internal company databases (*searched 22 November 2012*)		5	3

9.4.6 The inclusion and exclusion criteria.

Response

9.4.7 The data abstraction strategy.

Response

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

Saris 2009

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
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)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Bentley 2003		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Random sample numbers in sealed envelopes	Yes
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No comparison of patient demographics provided	Unclear
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)?	NA	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	Unclear

Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcome measures mentioned in methods were reported in results	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?	Unclear	Unclear
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
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)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See Appendix 2.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

A quality assessment was undertaken based on the STROBE checklist. If the study had provided the information then it was given a “Yes”, if not a “No”, or otherwise a “not clear” or not applicable

Table 59. Quality assessment of studies based on the STROBE checklist

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
1(a) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No
1(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2 Explain the scientific background and rationale for the investigation being reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3 State specific objectives, including any pre-specified hypotheses	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
4 Present key elements of study design early in the paper	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
8 For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9 Describe any efforts to address potential sources of bias	No	No	Yes	Yes	Yes	No	No	No	Yes	No
10 Explain how the study size was arrived at	No	No	No	Yes	Yes	No	Yes	No	No	No
11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
12(a) Describe all statistical methods, including those used to control for confounding	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(b) Describe any methods used to examine subgroups and interactions	NA	Yes	NA	Yes	Yes	NA	NA	Yes	NA	Yes
(c) Explain how missing data were addressed	No	No	No	Yes	Yes	Yes	No	No	No	Yes
(d) Cohort study—If applicable, explain how loss to follow-up was addressed	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
13(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
(b) Give reasons for non-participation at each stage	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No
14(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
15. Cohort study—Report numbers of outcome events or summary measures over time	NA	NA	NA	NA	NA	NA	Yes	NA	NA	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
16. (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(b) Report category boundaries when continuous variables were categorized	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Yes	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes

	Grade (yes/no/not clear/N/A)									
Criteria	**Bartlett 2005#(35)**	**Behrens 2006(41)**	**Genovese 2010(43)**	**Ebert 2011*(42)**	**Ebert 2012*(59)**	**Marlovits 2012(44)**	**Ventura 2012(45)**	**Zak 2012(46)**	**Vijayan 2014(47)**	**Nawaz 2014(48)**
18 Summarise key results with reference to study objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other evidence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21 Discuss the generalisability (external validity) of the study results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Modified version of the STROBE checklist

* RCT where both groups received MACI but different rehabilitation programs
# Prospective randomised study

Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

9.7.2 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

9.7.3 The date on which the search was conducted.

Response

9.7.4 The date span of the search.

Response

9.7.5 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.7.6 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.7.7 The inclusion and exclusion criteria.

Response

9.7.8 The data abstraction strategy.

Response

9.8 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

9.8.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Response

9.9 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Response

9.9.2 The date on which the search was conducted.

Response

9.9.3 The date span of the search.

Response

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.10 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		

27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.11 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Response

9.11.2 The date on which the search was conducted.

Response

9.11.3 The date span of the search.

Response

9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.11.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.11.6 The inclusion and exclusion criteria.

Response

9.11.7 The data abstraction strategy.

Response

9.12 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- NHS EED
- EconLIT.

Response

9.12.2 The date on which the search was conducted.

Response

9.12.3 The date span of the search.

Response

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.12.6 The inclusion and exclusion criteria.

Response

9.12.7 The data abstraction strategy.

Response

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

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

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

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