Protocol for TAR on ACI.

1. **Title:** Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee

2. **TAR team**

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3. **Plain English Summary**

Articular cartilage covers the ends of the bones, and the inner surface of the patella, in the knee joint. It should not be confused with the meniscal cartilages which are pads of cartilage between the bones – when people talk of "cartilage problems" in the knee, they often mean the meniscal cartilage.
Cartilage is a tough rubber-like substance that is normally very smooth, promoting smooth movements of the joints and also acting as a shock absorber. Under the articular cartilage are the bones of the knee – femur in thigh, tibia below the knee and the patella or knee-cap.
Cartilage once formed, is there for life. It has no blood vessels and has very limited ability to repair itself. Damage can lead to later osteoarthritis, and in some cases in the long-term, a need for a knee replacement with an artificial joint.

The cartilage cells are called chondrocytes. In autologous chondrocyte implantation (ACI), small pieces of cartilage are removed from the knee, and the chondrocytes are grown in the laboratory until they number millions. They are then put on to the damaged bit of articular cartilage as a sort of patch. The hope is that this patch will repair the damaged section and form a new layer of natural articular cartilage, called hyaline cartilage.

The main alternative method of repair is called micro-fracture, in which a small hole is drilled through the surface of the bone in the area of damaged cartilage, into the bone marrow, to let marrow cells infiltrate the area of damaged cartilage, where they turn into a form of scar cartilage called fibrocartilage. This is regarded as being inferior to hyaline cartilage, being less smooth and less hard-wearing, and it is not expected to last as long.

Microfracture may be combined with the insertion of a collagen membrane to cover the microfracture clot, known as augmented microfracture. This variant is more costly.

Microfracture can be done arthroscopically (i.e. without opening the knee joint) and could be done at the same time as debridement and lavage.

Another method, which is much less common, is mosaicplasty (sometimes called OATS – osteochondral autograft transfer system) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. The pieces are in little cylinder shapes and once transplanted, have an appearance not unlike a mosaic – hence the name. Mosaicplasty can only be used for small areas of damage (less than 4 cm) because the transplanted sections have to come from elsewhere in the knee. (In some countries, allograft cadaver donor tissue is used, but this does not appear relevant to the UK.)

4. Decision problem

NICE appraised ACI in 2005, and recommended that it be used only in research studies – it was felt that the evidence was insufficient to recommend use in the NHS. Since then the technology has evolved, and this appraisal will be of three forms of ACI;

- The ChondroCelect ACI system from TiGenix, in which the cultured cells are combined with a biodegradable collagenI/III patch. TiGenix call this characterised

chondrocyte implantation (CCI). Only one variant of ChondroCelect is used now – the seeded membrane technique.

- The Matrix ACI system (MACI – short for "matrix applied characterised autologous cultured chondrocyte implant") from Sanofi. The matrix refers to a collagen membrane with the chondrocytes.
- ACI wherein the cells are cultured in hospital or research laboratories, such as the RJAH hospital in Oswestry, termed "traditional ACI" in the NICE scope. This appears to be the only NHS facility that cultures cells. Traditional ACI is used under hospital exemptions from the advanced therapy medicinal products regulations.

With ACI, the cells can be protected by a cap, which can be periosteal (ACP-P) or collagen (ACI-C). Periosteal caps tend to cause hypertrophy of the cartilage graft which can cause catching of the knee and may require arthroscopic debridement. ACP-P is now little used in the UK and need not be considered in this appraisal. With MACI, the membrane is porcine I/II collagen, as is the dry membrane used in the Chondrocelect system.

Other technologies have been used but will not be considered in this appraisal. Section with examples removed

The decision to be made by NICE is whether ACI, in some or all of its forms, is clinically effective and cost-effective, and should now be used in routine NHS care. Both ChondroCelect and MACI have marketing authorisations, with slightly different indications. CCI is indicated for defects 0-5cm^2. MACI is indicated for defects of 3cm^2 or over.

5. Methods for assessing clinical effectiveness

Previous assessment report.

The last assessment report was done by the Aberdeen TAR team, but the principal authors are now with Warwick Evidence. This review will summarise the findings of the previous TAR and the current NICE guidance in the Introduction. Details of the trials reported in the 2004 report will be included in the clinical effectiveness section.

Patient group.

The patient group, as stated in the final scope from NICE, is "adults with a symptomatic cartilage defect (chondral defect) but without advanced osteoarthritis". The chondral defects can be on the femur, tibia or patella.

Osteoarthritis can be defined as generalised degenerative change affecting both sides of an articulation. ACI is used for isolated cartilage defects. There can be isolated defects on both surfaces ("kissing lesions") which could be considered for ACI if the rest of the joint is in good order, but our searches to date have found only trials in single defects. There is sparse evidence on the use of ACI in knees with osteophytes (which are a response to degenerative change). It is possible that ACI may have a place in early OA with focal damage.

People can have cartilage damage without symptoms, because there are no pain nerve endings in the surface of the cartilage. Symptoms develop when the underlying (subchondral) bone is affected.

No age restriction is given in the scope from NICE, but in past trials, patients had a mean age of 32, range 16 to 49, with about 60% men. In most cases, the cartilage damage was due to injury, usually from sport.
The EMA licence excludes advanced OA but not early OA. We note a paragraph that states that other knee conditions, including early OA, should be addressed first, which implies that some people with early OA can be considered for ACI. We do not think it is much used in OA, since that is usually defined as diffuse cartilage loss, but is a heterogenous condition. Generalised OA would not be suitable for ACI, but it might be considered in people with only focal cartilage damage, if supported by evidence.

Intervention

The intervention will be ACI for chondral defects in the knee only. (ACI has also been used in shoulder, elbow, ankle and hip problems.) The forms of ACI will be

- The ChondroCelect ACI, referred to by TiGenix as characterised chondrocyte implantation (CCI).
- The Matrix ACI system (MACI) from Sanofi.
- Traditional ACI.

Comparators

There are two other operations used to try to repair cartilage defects. These are microfracture and mosaicplasty, described above. Mosaicplasty is now in limited use,

for small defects. Osteochondral grafts from cadavers can be used but are not to any significant volume in the UK and will not be considered.

Knee replacement is included as a comparator in the NICE scope but we think this is inappropriate. The indications are very different. Knee replacement is mainly for advanced end-stage OA, performed much less often in people under 50 because the artificial knees do not last a lifetime, and would have to be replaced – and the second replacement may be a more difficult procedure than the first. People with articular cartilage damage are often quite young – sports injuries are a common cause, and mean age in past trials was 32. Occupational injuries are another. Knee replacement is not used in young people with isolated cartilage defects and so not a comparator, but rather a longer-term intervention if the damage leads to advanced osteoarthritis. It would not be used to treat an articular cartilage lesion in a young knee.

However, NICE have requested that knee replacement should be a comparator for larger lesions. We will search for head to head RCTs of knee replacement versus ACI but we do not expect to find such evidence.

Osteotomy is a procedure for people with single compartment damage, in which the tibia is divided (in effect broken) and reset in such a way as to shift weight-bearing away from the damaged area, and on to other parts of the articular surface. As mentioned in the NICE scope, this is used for larger areas of damage. We do not consider osteotomy to be a comparator, but ACI may sometimes be used in combination with osteotomy to realign a knee, where the biomechanics of the knee need to be restored to avoid the ACI being sheared off. We will not include osteotomy on its own as a comparator. However it may feature in modelling since it can be used to postpone knee replacement in younger people. If ACI is successful, the costs of osteotomy may be avoided.

Lavage and debridement is a process involving washing out the knee joint to remove debris (lavage) and fragments of loose cartilage (debridement). Its effectiveness in relieving symptoms is in doubt (Moseley et al 2002), and it is not a way of repairing cartilage. So if used, it would be a precursor to ACI, rather than a comparator.

The NICE scope includes “best supportive care” which we take to be non-operative intervention, including symptomatic relief from analgesics such as paracetamol and non-

steroidal anti-inflammatory agents, and rehabilitation interventions such as physiotherapy. There is a useful review of physiotherapy at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3204363/

Newer partial replacements such as synthetic patches for small defects, such as Hemicap, BioPoly, and Episealer, will not be considered in this NICE appraisal.

In summary, the main comparator is microfracture, for any size of lesion. Mosaicplasty is less used, but remains a comparator for small lesions. Best supportive care could also be a comparator, though by the time patients are referred for consideration for ACI, they have usually failed on best supportive care.

Treatment pathway.

The treatment pathway might involve;

- Persistent pain and limitation of activities such as sport, despite symptomatic treatment and physiotherapy. Symptoms include pain, locking, and the knee giving way, and can impair quality of life as much as osteoarthritis.
- Referral to Orthopaedics
- Investigation, usually an MRI scan first, then arthroscopy, and often debridement and lavage.
- A regenerative procedure, such as ACI or microfracture

Outcomes

These are as in the NICE scope;

- 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.

The commonest adverse event is failure to repair the area of damaged cartilage.

A number of clinical outcome measures are used in knee problems, including;

- the Lysholm score, with a range of 0 to 100, based on 8 aspects: pain, limping, locking, stair-climbing, need for supports, instability, swelling and squatting.
- The Tegner score of activity, range 0 to 10.
- The Knee Injury and Osteoarthritis Outcome Score (KOOS) which assesses pain, symptoms, activities of daily living, sport and recreational activities, and knee-related quality of life, with scores of 0 (worst) to 100.
- Cincinnati knee score for symptoms (pain, swelling) and function (walking, climbing stairs, running) with a score of up to 100.
- Other scores used less often are the International Knee Documentation Committee (IKDC) score and the Meyers score.
- Generic scores such as SF-36, SF 12 and EQ-5D, and visual analogue pain scores.

The International Cartilage Repair Society (ICRS) score assesses quality of tissue repair rather than patient reported outcomes. It could be argued that the quality of tissue repair might be useful for extrapolating from short-term histological results to long-term osteoarthritis and need for knee replacement, but the key outcome is symptoms and there is far from perfect correlation between symptoms and the degree of OA.
Imaging techniques may also provide interim data, and include MRI scans and plain X-rays, the latter including the Kellgren and Lawrence system for grading osteoarthritis, which correlates with knee pain.

Problems
The main problem is likely to be the requirement to extrapolate from short-term outcomes in trials, to long-term results, including the need for knee replacement.
In some studies in the past, biopsies on the cartilage repair have been done, to show whether the repair has generated hyaline cartilage or fibrocartilage. The consensus is that hyaline gives a much better result, but we will need to examine the evidence base for this. We will seek evidence on the relative longevities of the two forms, and

whether symptoms are less troublesome in the long-term if there is hyaline cartilage rather than fibrocartilage. However differences in outcomes between hyaline and fibro-cartilage may not be significant for 5-10 years (MSAC 2011) which has implications for the length of follow-up required to provide good data. In addition, ACI takes about 3 years to form highly organised hyaline cartilage so earlier biopsies may give a misleading picture.

Search strategy

The search strategy is attached as appendix 1. Searches will be run in Medline from 2010 to present and adapted to as appropriate for the databases Embase, Cochrane Library and Web of Science. Searches will not be limited by language. A scoping search showed that the only language other than English that has a significant number of studies is German. There will be checked and included if useful. The date, 2010, is based on the Cochrane review.

Our scoping search also showed there to have been about 30 reviews since 2004. The reference lists of the most recent ones will be checked.

In addition, we will ask NICE to contact the ACTIVE trial group, asking if they will release data on interim outcomes. (www.active-trial.org.uk). However the first analysis from ACTIVE is scheduled to be after all recruits have had 3 years of follow-up, and this may not be till December 2014. The last 10-year follow-up visits will be in December 2021. It therefore seems unlikely that the 3-year data from ACTIVE will be available in the current NICE timelines.

Types of studies

For comparing effectiveness, we will rely on RCTs, including looking for longer-term follow-up data from the trials include in the last review (Bentley, Horas, Knutsen, Basad), and adding new trials. For longer-term data, adverse events and costs, we will also consider observational studies with at least 50 participants and follow-up of over 3 years.

Study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

High quality recent reviews will be appraised and conclusions summarised. We will also check any relevant clinical guidelines.

Data extraction strategy

Data will be extracted by one reviewer and checked by a second using a standardised data extraction form. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and checked by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted.

The Coleman score will be used, for both RCTs and observational studies.

Methods of analysis/synthesis

If data permit, we may carry out a meta-analysis using Review Manager.

Methods for estimating qualify of life

We will look for generic health status data such as EQ5D or SF36 data. Where condition-specific data are presented, we will search for tools for generating generic data from the condition-specific results.

Subgroups

If data permit, sub-groups to be examined may include;

- By duration of symptoms. NICE suggest duration of less or more than 3 years. In early trials, duration was often much longer. For example, the average was 7 years in the Bentley trial, but that was done when ACI was a new technology, and most patients had had previous treatment. We will decide on duration sub-grouping once we have reviewed the evidence. Earlier treatment is likely to be more effective, because longer duration of chondral defects increases the chance of degenerative change.
- Size of lesion
- Previous surgery such as microfracture. It has been suggested that ACI may be more successful if used as first treatment.
- NICE also suggest cartilage defects secondary to mal-alignment. This may not be possible since in past trials, most cartilage defects have followed injury.

- Possibly, non-traumatic causes such as osteochondritis dissecans, if numbers permit and results are presented separately.
- Possibly, patients with early OA, if numbers permit, it is clearly defined, and results are given separately. Patients with OA are usually excluded from trials but we note a systematic review of nine case series in early OA (de Windt et al 2013).
- Possibly, groups by aetiology (sports or occupational injury) since the level of activity after repair procedures may affect longer-term outcomes.

6. Report methods for synthesising evidence of cost-effectiveness

Cost-effectiveness of ACI will depend on short-term benefits such as relief of symptoms and hence quality of life, and on longer-term functioning and health status, and avoidance of knee replacement. The main problem in the economics analysis may be the lack of long-term outcome data from the trials, and hence the need to extrapolate from short-term results to long-term functional status and quality of life, and the need for knee replacement..

Literature review

A comprehensive literature review for published cost studies, quality of life (utility) studies, and economic evaluations (including any existing economic models) of ACI will be conducted. In addition to the clinical databases such as Medline, we will search the economics literature (such as NHS EED, Web of Science, CEA registry). The search terms will include the appropriate clinical terms, in conjunction with the appropriate economic terms. The search strategy will start from dates in the previous TAR. Data will extracted by one reviewer and checked by a second, using a standardised data extraction form for the economic studies. Any discrepancies will be resolved by discussion. If this is not feasible, a third reviewer will be consulted. We will use the CHEERS checklist (Husereau et al, 2013) to assess the quality of the economic evaluation studies and any models will be further assessed using the quality assessment of economic modelling checklist developed by Phillips et al (2004).

Economic model

a) Model structure, time horizon and transition probabilities

Depending on the results from the literature search we may have to develop a *de novo* economic model. A Markov-decision type model would be constructed to estimate

the cost-effectiveness of ACI. The perspective will be that of the National Health Services and Personal Social Services. To assess the cost-effectiveness of ACI comparisons, two main comparisons will be undertaken:

1) If data permit, we will compare the different forms of ACI with each other; and
2) We will compare ACI with micro-fracture and mosaicplasty.

We will construct two models using an appropriate cycle length: 1) a short-term model (probably 3 years, but to be decided in the light of the clinical effectiveness evidence) looking at the short-term benefits such as pain and quality of life; and 2) a long-term model to estimate the cost per quality-adjusted life year (QALY) gained from ACI. The time horizon of our long-term model will be 40 years in order to reflect the long-term effect on knee replacement.

The model will incorporate adverse effects specific to ACI such as pain, joint swelling, tissue hypertrophy, and failure of procedure. Rarer events such as infection and deep vein thrombosis will also be considered. It will include progression to TKR, or to uni-compartmental knee replacement, impacts on quality of life and natural mortality. If evidence permits, the economic model will be conducted for different age groups. The Australian report (MSAC report, 2010, p10) suggests that ACI is not performed in patients aged 55 years and above, but does not make it clear why. If someone aged over 50 has an isolated chondral defect in the absence of OA, there seems no reason why a regenerative procedure should not be performed. However it may be that chondrocytes extracted from older people are more difficult to culture in vitro. (There may be laboratory data on this.) Conversely, younger people with poor quality of life may receive knee replacements at ages younger that the usually accepted minimum age of 50.

Information from the clinical effectiveness review will help determine the probabilities for each pathway and also the success rates of ACI and revision rates for further ACI. Sensitivity analyses will be used in areas of uncertainty.

a) *Identifying resource use, costs and utilities:*

Information on resource use and costs associated with the different pathways (e.g. different ACI treatment, theatre time, drugs, staff time etc.) will be collected from a systematic review of the literature and from expert clinical advice. Any remaining gaps for resource use parameters will be filled by consulting experts or by assumptions made by the research team.

Unit costs will be based on national data where possible. For example, in the base case, costs of the different ACI procedures will be based on list prices from the NHS supply chain and from NHS reference cost data [NHS Reference costs]. However we know that substantial, but confidential, discounts are available, linked to volume, and this will be addressed in sensitivity analyses.

Reduced costs might be expected if more hospitals provided a cell culture service, such as in Oswestry, but Oswestry is currently the only NHS site with MHRA exemption. Other centres with appropriate facilities have expressed an interest in culturing their own cells.

Costs of consultations with secondary care staff will be drawn from Unit Costs of Health and Social Care [PSSRU] Drug costs will be obtained from the British National Formulary.

Effectiveness and utility data, including ACI adverse effects (and disutilities associated with the treatments) will be derived from the literature review. Experience from the previous TAR highlighted that evidence on the quality of life gains from treatment with ACI was limited. If direct measurements of utility or choice-based multi-attribute utility scales (such as the EQ-5D or SF-6D) suitable for calculation of QALYs are not reported we may need to use one of the algorithms for mapping from a clinical measure (e.g. Oxford Knee Score) to a measure of utility. If insufficient information is available for utilities it may have to be elicited from an expert clinical panel or by assumptions made by the research team.

b) Analysis:

Both costs and QALYs will be discounted at 3.5%. It should be noted that if ACI prevents knee replacement, the costs avoided will be much reduced by discounting. The results of the model will be presented as an incremental cost per QALY gained for each treatment compared with the next best alternative.

We will use both simple and probabilistic sensitivity analysis to explore the robustness of the results and to estimate the impact of uncertainty over model parameters. The simple sensitivity analysis will be used to assess the robustness of the results to changes in deterministic parameters such as costs, utilities and the discount rate. The results from the probabilistic sensitivity analysis will be presented as cost-effectiveness acceptability curves.

A sensitivity analysis will be carried out using a reduced cost, such as might be expected if more hospitals provided a cell culture service, such as in Oswestry.

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 26th August 2014. Data arriving after this date will not be considered, unless submitted in response to clarification questions. (Note that since this is an MTA, based principally on the TAR team's report, there may be no clarification questions.) If unpublished trial or other data meet the inclusion criteria for the review they will be quality assessed and extracted as outlined above. Any economic evaluations provided by manufacturers will be compared with the TAR team's analysis, and reasons for any differences will be explored, such as assumptions about clinical effectiveness and costs. Detailed critiques of manufacturer models, as done in STAs, will not be carried out.

Any 'commercial or academic in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report.

8. Competing interests of authors

None.

9. Advisory panel

Expert advice is being provided by

Leela Biant, consultant trauma and orthopaedic surgeon, Edinburgh

Paresh Jobanputra, consultant rheumatologist, Birmingham

We await agreement from a second orthopaedic surgeon to be named as expert advisor.

10. Timetable/milestones

This protocol takes account of comments from expert advisors and colleagues at NICE. It will be finalised after discussions at the consultee information meeting on 11th June.

We will submit the final TAR by 25th November, to NICE and NETSCC.

Appendix 1. Search strategy

The search strategy (below) will be run in Medline from 2010 to present and adapted as appropriate for the databases Embase, Cochrane Library and Web of Science. Searches will not be limited by language. We anticipate a need to use some German language papers.

1. exp Chondrocytes/tr [Transplantation]
2. exp Cartilage, Articular/tr [Transplantation]
3. (chondrocyte* adj2 implant*).tw.
4. (chondrocyte* adj2 transplant*).tw.
5. (autologous adj3 transplant*).tw.
6. (autologous adj3 implant*).tw.
7. (MACI or chondrocelect or ACI).tw.
8. (cartilage* adj2 transplant*).tw.
9. (cartilage* adj2 implant*).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Knee/ or knee.mp.
12. 10 and 11
13. exp Transplantation, Autologous/
14. exp Cartilage, Articular/su [Surgery]
15. exp Chondrocytes/tr [Transplantation]
16. 14 or 15
17. 13 and 16
18. 12 or 17

19. limit 18 to yr="2004 -Current"

Meeting abstracts will also be searched, including those from the Oswestry Cartilage Symposium, British Association for the Surgery of the Knee (BASK) Annual Meeting, European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) Congress, American Association of Hip and Knee Surgeons (AAHKS) Annual Meeting.

The websites of the European Medicines Association (EMA), the Food and Drug Administration (FDA) and other HTA agencies will be searched for relevant assessment reports.

Searches for ongoing or recently completed studies will also be performed in the databases ClinicalTrials.gov, Current Controlled Trials, World Health Organization Clinical Trials Registry Platform Search Portal and UK Clinical Research Network Study Portfolio.

In addition, the inclusion lists of recent systematic reviews will be checked. Experts such as the ACTIVE trial group may be contacted for unpublished data, with reassurances that data would be treated as academic in confidence and redacted from any documents placed in the public domain.

Auto-alerts in Medline and Embase will be run for the duration of the review to ensure that newly published studies are identified.