ACTIVE

AUTOLOGOUS **C**HONDROCYTE **T**RANSPLANTATION / **I**MPLANTATION **V**ERSUS **E**XISTING TREATMENTS

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1. ABSTRACT

ACTIVE is a prospective randomised trial comparing cell grafting techniques for the repair of articular cartilage in the knee (autologous chondrocyte implantation (ACI) or matrix-induced ACI (MACI)) with standard treatments for patients who have had a failed primary treatment for chondral or osteochondral defect(s) in the knee.

The target recruitment is at least 480 patients over 5 years. Thirty centres (28 in the UK, 2 in Norway) have so far agreed to participate.

Patients will be randomised to either ACI (surgeon can choose either ACI or MACI or a sub-randomisation between two types of matrix-assisted ACI: MACI and Chondron) or standard treatment

Investigators choosing traditional ACI have the option of further randomising patients to have a patch made of (a) periosteum or (b) collagen membrane.

The choice of cell grafting technique and standard treatment will be pre-specified by the recruiting surgeon, individually for each patient.

Patients in the Standard treatment arm may have debridement, abrasion, drilling, microfracture, mosaicplasty, or AMIC according to clinical indication.

The joint primary outcome measures will be time to cessation of benefit of treatment and patient-reported Lysholm score.

Secondary outcomes will be functional knee scores (assessor completed Lysholm, Cincinnati, IKDC) and Quality of Life measures (EQ5D) at intervals up to 10 years post operation.

Health economic analysis is an integral part of the study.

2. BACKGROUND TO TRIAL

2.1. Chondral lesions

Articular cartilage provides a smooth, low-friction surface in the knee joint and dissipates the compressive and shear forces generated by movement under load. High, supra-physiological loading can fracture the joint through the cartilage or through the sub-chondral bone, giving rise to chondral or osteochondral defects, respectively. Such injuries are most commonly sustained as a result of sporting injury or trauma. In the condition osteochondritis dissecans (OCD), loss of a fragment of cartilage or bone and cartilage appears to occur spontaneously without trauma.

Patients who experience symptoms after cartilage injury complain of knee pain, knee swelling, joint locking, and instability. The inability to work and play sport severely diminishes the quality of life of these patients. The long-term sequelae are not well documented although 55% of OCD patients who sustained joint damage as young adults went on to develop severe osteoarthritis earlier than patients with idiopathic OA (1). This is an important point, for although arthroplasty is an excellent procedure in the elderly (>60 years), the failure rate in younger patients is much higher - 20% failure in the first 10 years, 49% within 20 years (2). Effective early treatment of these defects would reduce disability and may prevent early onset osteoarthritis secondary to these conditions, so eliminating or postponing the need for joint replacement and reducing the likelihood of revision arthroplasty.

Currently there is no uniform approach or gold standard for the management of hyaline cartilage defects in the knee. Good results following simple debridement were reported in 60% of cases at 5 years (3). Replacement of the cartilage with synthetic materials (e.g. carbon fibre) does not provide a permanent solution. In other surgical procedures, termed marrow stimulation techniques (drilling, abrasion, microfracture), the base of the debrided defect is breached to cause bleeding of the bone and clot formation in the defect. The clot becomes populated with bone marrow stromal cells from the intra-trabecular space of the subchondral bone that produce a fibrocartilaginous matrix. As this does not have the hyaline structure of normal cartilage, there is some question as to how long this can withstand the stresses of joint movement, however good outcomes up to 7 years after surgery have been reported (4). Transfer of osteochondral grafts from minor load bearing parts of the joint into the defect (mosaicplasty) has also been shown to be effective for smaller defects up to 4cm^2; (5) but this procedure is not recommended for larger lesions.

2.2. Autologous chondrocyte implantation

In recent years, autologous chondrocyte implantation (ACI) has been used increasingly for the treatment of chondral and osteochondral defects (6). In this procedure, a small sample of cartilage is removed from a minor load bearing part of a patient's damaged joint; chondrocytes are isolated from this and grown in monolayer culture in vitro. When the cell number has been amplified sufficiently (3-5 weeks to generate 8-12 million cells), cells are implanted into the debrided defect in a second planned operation. The cell suspension is retained by a

membrane, which may be either periosteum or a collagen membrane, sutured to the edges of the defect and sealed with fibrin. This procedure has the potential to generate repair tissue that is well integrated with the surrounding cartilage and offers a durable surface. With up to eleven-year follow up of patients who have had this procedure, good to excellent outcome has been reported in approximately 80% of patients, depending on the anatomical location of the defect (7). Importantly, histological analysis of the repair tissue after ACI shows features characteristic of hyaline articular cartilage (7, 8, 9, 10).

Many surgeons and patients have great expectations of ACI. More than 12,000 people have now received ACI world-wide. However, as yet, the long term benefit of ACI over other treatments has not been conclusively demonstrated. The study with the longest follow up (7) shows continuing benefits from ACI after eleven years, but with no comparator group. However, two recent small-scale short term studies have reported that microfracture (11) or mosaicplasty (12) give results as good as or better results than ACI. A third study reported the outcome of ACI to be better than mosaicplasty (13).

The original ACI procedure made use of the patient's own periosteum to cover the defect and retain the implanted cells. More recently decreased morbidity has been reported using a membrane made from porcine collagen membrane (8, 13). A further development of the ACI procedure is to seed the cells onto the collagen membrane in the laboratory, and at the second stage the seeded membrane is attached over the defect using fibrin sealant. This technique known as matrix-induced ACI (MACI®) (provided by Genzyme) can be performed via a mini-arthrotomy, thus saving operating time and offering a less invasive alternative to ACI. One-year follow-up results of a study by the Stanmore Group (14) suggest ACI and MACI® provide a similar clinical outcome.

A further matrix version of ACI is Chondron™ provided by Sewon Cellontech. With Chondron™ the cells are suspended in a gel which acts as a scaffold for holding the cells within the defect, thus avoiding the need for a patch or sutures. Chondron has been applied to more than 1500 patients in.

Previously the ACTIVE trial was designed to include only ACI. However, following Main Research Ethics Committee (MREC) approval in March 2007 the use of MACI® or ACI (according to surgeon preference) is allowed in the ACI arm of the trial and following MREC approval in March 2008 Chondron™ is an allowable option. If used, Chondron will be sub-randomised against MACI® within the ACI arm of the trial. In this document all references to the ACI treatment arm should be interpreted as meaning ACI or MACI/Chondron.

In December 2000, the National Institute for Clinical Excellence (NICE) published guidance on the use of Autologous Cartilage Transplantation for full thickness cartilage defects in knee joints (Technology Appraisal Guidance no 16). The guidance recommended an adequately powered, randomised trial comparing ACI against the best alternative treatment for patients who have had a previous simple debridement that has not relieved symptoms. A further recommendation was that robust cost effectiveness studies should also be carried out. This guidance was

updated in 2005 making it clear that every patient treated with ACI should be enrolled in a clinical study designed to generate robust and relevant outcome data.

In 2003, The Medical Research Council agreed to fund, and the Department of Health agreed to support the present trial called ACTIVE - **A**utologous **C**hondrocyte **T**ransplantation / **I**mplantation **V**ersus **E**xisting standard treatments.

2.3. Aims of the trial

The ACTIVE trial aims to find out if there is a clinical benefit of ACI compared with any of a range of non-cell grafting techniques that the surgeon considers is the best alternative. This flexibility allows the wide range of individual factors in a patient with a chondral defect of the knee, which has already failed previous treatment, to be taken into account. Surgeons can choose the type of surgery with which they are most accustomed or which they personally consider to give best results. In order to avoid potential biases and so that trial analyses can be stratified by the type of control intervention that would have been received, the intended control procedure will be asked at randomisation.

Surgeons may opt to further randomise ACI patients in order to compare the patient's own periosteum with collagen membrane for retaining the cells.

Surgeons recruiting patients to this study must have an open mind and be undecided whether any of the trial treatments is a clear benefit over one of the alternatives for the particular patient. Patients must be appropriate for ACI or one of the alternatives. As ACI involves 2 procedures and both ACI and mosaicplasty involve significant surgery, patients should have symptoms that warrant such treatment.

Originally patients with osteochondral defects (OCDs) defined as bone loss exceeding 3mm depth, were excluded from the trial. However, in recent years bone grafting techniques have developed to the point where the bone can be successfully restored and a cartilage regenerative treatment can be attempted as part of the same procedure. Therefore, as of March 2008 this protocol includes OCDs provided the surgeon carries out a bone grafting technique aimed at restoring the bone to within 3mm of the surrounding bone. Patients with a chondral defect exposing bone on the tibia are excluded. Patients where osteotomy of the femur or tibia or meniscal transplant is planned will also be excluded. These patients are better studied separately.

The randomisation process will take into account factors that might affect outcome and, to avoid the possibility of bias, the outcome will be assessed by an independent observer who has no knowledge of the treatment allocation, through structured questionnaires and functional assessments.

Previous studies of ACI have focused on an improvement in functional knee score. In ACTIVE the principal outcome will be the survival of any benefit. The definition of failure will be the point at which the patient's symptoms or activity level have not improved, or are worse. The first time point for measuring cessation of benefit will be 3 years post treatment. A detailed health economics analysis will take into account the cost of different treatments allocated.

3. TRIAL DESIGN

The main question being addressed by ACTIVE is:

- does ACI offer a better clinical outcome at 3, 5 and 10 years post-operation than alternative procedures for the repair of isolated chondral defect(s) of the knee that remain symptomatic following previous treatment?

The question will be addressed by direct comparisons between patients allocated ACI and patients allocated a pre-specified control intervention not involving ACI.

The target is to recruit at least 480 patients in up to 30 centres (28 in the UK and 2 in Norway) over 5 years.

3.1. Large, simple trial: minimal extra investigations and data collection

To make large-scale recruitment feasible, the ACTIVE trial is "streamlined" so as to impose as little extra workload on clinicians as possible, beyond that required to treat their patients. The single test used for assessing eligibility for the study is one which would be used in standard practice for patients due to receive ACI, and the important prognostic information will be collected at randomisation. Many of the scales used are patient rated, and cessation of treatment benefit will be assessed by a blinded assessor provided by the study.

3.2. Randomised comparison of ACI versus a preferred control option: eligibility based on uncertainty

There is no general consensus as to which patients are likely to derive the most benefit (if any) from ACI. In addition, the patients who may be eligible for ACI therapy are a heterogeneous group, and the therapy which they would receive in the absence of ACI may vary. Not all procedures are suitable for all types or sizes of chondral defect, and there may be understandable reluctance to randomise patients to receive a treatment that has already failed. For this reason, ACTIVE adopts a flexible pragmatic design in order to assess the relative efficacy of ACI in a clinically wide population of patients.

In ACTIVE, therefore, eligibility is based not on rigid entry criteria but on the "uncertainty principle". That is, if the doctor or the patient considers, for any reason, that there is a definite indication for, or a definite contraindication against ACI then the patient is not eligible for ACTIVE. If, on the other hand, both doctor and patient are substantially uncertain whether or not to use ACI then that patient is eligible to be randomised between ACI and another procedure (if the patient also meets the criteria listed in Section 3.1.) In these circumstances, randomisation is both scientifically and ethically preferable to the uninformative alternative of not randomising and treating the patient in an *ad hoc* way outside of a study. Eligibility based on uncertainty has been used in several previous trials e.g. the "ISIS" trials, the MRC International Stroke Trial, and the MRC QUASAR trial (QUASAR Collaborative Group) (15) and has been shown to simplify trial procedures and to facilitate large-scale recruitment of an appropriately heterogeneous group of patients. The decision on whether the indication is uncertain, and the criteria on which it is based, are left entirely to the responsible physician. Even within one participating hospital different doctors may decide

differently as to the categories of patient for whom the indication for ACI is uncertain.

4. PARTICIPANT SELECTION AND ENROLMENT

Potential eligible patients will normally be identified by the surgeon at the out-patients clinic where interested patients will receive a Patient Information Leaflet (Appendix 1). At this stage the surgeon will complete Parts A&B of the Patient Entry Form (Appendix 2) and pass this form on to the study coordinator. At the next out-patient appointment or at a separate visit the study coordinator will see the patient to ensure he/she is fully informed about the trial. If the patient agrees to participate in the trial he/she will sign a consent form (Appendix 3). The study coordinator will then complete all questions in Part C of the Patient Entry Form (Appendix 2).

4.1. Simple eligibility: symptomatic chondral defect, failed previous procedure, no "definite" indications for, or "definite" contraindications against ACI

To encourage widespread recruitment, the eligibility criteria are made deliberately pragmatic. A patient is eligible for the trial if:

- the patient is not participating in any other clinical trial involving the knee, either currently or in the last 6 months
- there is a symptomatic chondral defect on the medial or lateral femoral condyle or trochlea, or patella needing surgery. Patients with 2 defects in the same compartment may be included if the defects are to be treated in the same way.
- the defect is considered suitable for ACI and at least one of the existing alternative treatments
- there has already been a previous procedure (which may be arthroscopic washout or ACI) carried out on the same defect at least 6 months previously which has failed to relieve symptoms
- there is substantial uncertainty as to whether to treat with ACI or with conventional therapy
- the patient is shown to be negative for serology tests required by the cell provider. This includes HIV, hepatitis B and C, syphilis, and may also include human T cell lymphotrophic virus (HTLV) I and II.
- For any eligible non-English speaking patients translation services will be employed as and when necessary.

Not all defects are necessarily associated with a likelihood of worthwhile benefit and the following list includes conditions where ACI would not be considered helpful in treating a knee defect. There are also some contraindications to ACI therapy. Thus, a patient is ineligible for the study if subject to any of the following:

- a defect of greater than 12 cm^2 in total area
- total meniscectomy, or untreated malalignment of the patella
- osteoarthritis, inflammatory condition, history of mesenchymal tumours
- known anaphylaxis to any product used in chondrocyte preparation

- low probability of compliance with physiotherapy or follow-up, including a major life-threatening condition.

4.2. Central randomisation:

Randomisation will be performed centrally by the University of Birmingham Clinical Trials Unit (BCTU) and patients can be entered either by telephone (Freephone 0800 953 0274 within UK, +44 (0) 121 687 2319 elsewhere), Fax (+44 (0) 121 687 2313) or over the internet (https://www.trials.bham.ac.uk/active). The Local Co-ordinator will need to provide all necessary details about the patient and reference to the Patient Entry Form (Appendix 1) beforehand may be helpful in preparing for randomisation.

To ensure balance between patient groups, treatment allocation will be by minimisation, with stratification variables:

- intended control treatment option
- size of chondral defect
- age
- pre-operative functional knee score
- femoral or trochlea/patella defect.

Randomisation will not be stratified *a priori* by centre, as this can lead to unacceptably high rates of prediction of future treatment allocations, thereby introducing potential selection bias (16). Instead, centre effects will be investigated by *post hoc* stratification of analyses.

In order to reduce the possibility of bias that may be introduced because of different waiting times for different operations, randomisation should take place as close as possible to the intended time of operation. It is recognised however, that certain centres may have difficulty in managing their caseloads with the uncertainty of whether a patient will be requiring ACI or a potentially shorter operation. In order, therefore, to ensure that resources are not under-utilised, there will be the option of a pairwise randomisation (17). Clinicians may choose to randomise two patients simultaneously, in the knowledge that one patient will receive ACI and the other will not. This procedure is currently in use with good results in the MRC-funded PD-SURG trial.

If it is anticipated that there will be a delay in treatment (i.e. more than 6 months), the patient details will be registered and the Trial Office will then contact the local co-ordinator nearer the time of surgery. If the patient remains eligible for the study, and surgery is anticipated within three months, randomisation will then occur and the allocated procedure advised. Delaying randomisation will minimise pre-treatment drop-out after randomisation which would dilute the power of the study.

The patient's GP will be informed of the treatment allocation (appendix 4).

5. SURGICAL TECHNIQUES

5.1. Debridement

An essential feature of debridement is removal of all “unstable” cartilage from the edge and base of the defect which is then washed away. In a randomised trial comparing arthroscopic washout with debridement for isolated medial femoral condylar lesions, good results for debridement were reported (3).

5.2. Abrasion/drilling

In addition to removing loose fragments as in debridement, the base of the defect is debrided until small bleeding points are seen. This bleeding is best confirmed with the tourniquet down.

5.3. Microfracture

This technique was introduced 20 years ago and is a modification of the drilling technique. Advantages of microfracture over drilling are that no over-heating or burning of the subchondral bone is created. The first step is accurate debridement of all unstable and damaged cartilage in the lesion including the calcified layer down to the subchondral bone plate. All loose or marginally attached cartilage from the surrounding rim of the defect is also debrided to form a stable perpendicular edge of healthy cartilage. An arthroscopic awl is then used to make multiple holes in the defect, 3-4 mm apart, but not so close that they could break into each other, as the subchondral bone plate should be kept intact. It is also easier with a curved awl compared to a drill to penetrate the defect perpendicular to the surface during an arthroscopic procedure.

Following microfracture the defect is filled with a so- called “super clot”. This is the key to the entire procedure and this clot is believed to be the optimal environment for the body’s own pluripotential marrow cells to differentiate into stable tissue within the lesion. Acceptable clinical results up to 5 year and then a decline have been reported for most marrow-stimulating techniques for cartilage repair (18). However, Steadman (4) recently published outcomes of microfracture for traumatic chondral defects in which 7 years after surgery, 80% of the patients rated themselves as improved.

5.4. Autologous Matrix Induced Chondrogenesis (AMIC®)

AMIC® has recently been marketed as a new technique that aims to improve on microfracture by using Chondro-Gide® membrane to hold the “super clot” in place, providing a matrix for new cartilage tissue formation (19, 20). The membrane is attached with fibrin glue or sutures via an arthrotomy.

5.5. Mosaicplasty

The technique of Mosaicplasty or Osteochondral Cylinder Transplantation (OCT) was first described by Matsusue et al (21) in 1993. In the technique, osteochondral plugs are taken with a cylindrical cutting device and used to fill the cartilage defect. Plugs are usually taken from the peripheries of both femoral condyles at the level of the patellofemoral joint and replaced as a "mosaic" to fill the defect. The technique is usually done as an open procedure in all but the smallest defect as care has to be taken that the harvest site matches the donor site for its contour

and thickness of cartilage. Plugs should be tightly fitting so that they do not later loosen. Healing of the donor site is usually good.

The main advantage of this technique is that treated defects are filled with mature hyaline cartilage straight away. The disadvantage is donor site morbidity, which limits the size of defect that can be readily repaired to 1-4cm^2. In larger defects where multiple plugs are used, there may be lack of congruity between the edges of the plugs and gaps between plugs may allow synovial fluid to escape and cause cyst formation.

The largest single series to date is that of Hangody (5) who described good to excellent results after 10 years in 92% of patients undergoing mosaicplasty of the femoral condyle.

5.6. Autologous Chondrocyte Implantation (ACI)

The technique of Autologous Chondrocyte Implantation was first described by Brittberg et al in 1994 (4). In ACI, culture-expanded autologous chondrocyte cells are injected into a chondral defect underneath a patch of periosteum. A number of studies, including long-term follow up in the Swedish study, have been encouraging with reports of over 80% of patients having excellent or good results at 5-11 years after ACI (6).

In ACI stage 1 (arthroscopic) a harvest of articular cartilage is taken and sent to the laboratory for cell preparation. The protocol of the cell supplier must be followed carefully. It is essential that sufficient cartilage is harvested to allow the chondrocyte culture to be established. All the cultivated cells are used for the implantation and therefore no cells are stored for any other purpose. While most surgeons take the cartilage harvest from the upper medial femoral condyle, recent research (22) suggests that cell yield is comparable from harvests taken from the lateral ridge, trochlea or intercondylar notch. Different instruments (ronger, rasp, curette, gouge) may be suited to different sites.

In ACI stage 2, which is usually carried out as an open procedure 3-4 weeks later, the edge of the defect is debrided until stable cartilage is obtained. Care is needed at the leading edge of a defect as there can be detachment of cartilage from subchondral bone that is not readily apparent. The base of the defect is debrided with care to avoid bleeding. Internal osteophytes can either be excised with a sharp osteotome or impacted with a punch. Bleeding from bone can be inhibited by an adrenalin solution.

To harvest periosteum an oblique incision is made in the line of the intrapatellar nerves below the joint line. This exposes the anteromedial tibia just below the pes anserinus. A template (e.g. suture pack foil) of the size of the defect is generally used and applied to the periosteum and an incision is made 2mm outside the edge of the endplate with a fresh 15 blade. This is then raised with a fine periosteal elevator. The periosteum is cleared of all fat and transferred without delay to the chondral defect, with the cambium layer facing in towards the defect. The periosteum must not be allowed to dry out. Collagen membrane should be used only after training and according to the manufacturer's instructions. Sutures placed in opposite corners initially helps to keep the membrane/periosteum central.

Interrupted sutures, 3mm apart, are most generally used. In the case of large defects extending to the edge of a condyle it may be necessary to use a 'K' wire and drill holes through bone to hold sutures. Fibrin glue is applied to the edge of the defect and the patch then tested for `water-tightness'. When satisfactory, the volume of cells recommended by the supplier is then inserted under the patch and the wound is closed.

For matrix-induced ACI and Chondron stage 1 is carried out as described above for ACI. Once at the laboratory the cells for MACI are grown onto collagen membrane for 3-4 weeks. Stage 2 is performed via a mini-arthrotomy in which a template of the defect is made and used to cut the seeded membrane to size. Fibrin sealant is applied to the subchondral bone plate and the MACI® membrane is sealed into position using gentle pressure. With Chondron the cells are expanded then mixed with a tissue fibrin sealant and this mixture is injected over the defect.

5.7. Post operative rehabilitation

Appropriate post-operative rehabilitation is essential whichever treatment is allocated. Recommended protocols for each of the treatment options will be made available.

As the aim of debridement is symptomatic relief rather than tissue regeneration, there is no need for protected weight-bearing, hence post operative rehabilitation is with crutches and full weight-bearing as able to ensure return to full function.

Following abrasion, drilling, microfracture, AMIC or mosaicplasty, immediate post operative continuous passive motion (CPM) and restricted weight bearing to protect regenerating tissue is recommended for all patients. After ACI, MACI or Chondron 6 hours post–operative rest allows for cell adherence. This is followed by CPM for 3 days and restricted weight bearing with crutches for up to 8 weeks. An exercise bike is a good way for all patients to continue with CPM. The idea is for them to spin against low resistance for an hour a day or more.

6. REGULATIONS AND TRAINING

6.1. Cells

The autologous chondrocyte preparations used in this trial must be produced in accordance with the Code of Practice for Tissue Banks published by the Department of Health (February 2002) or under an accredited GMP scheme for human somatic cell therapies.

The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that chondrocytes are not regarded as a medicine under current legislation, thus it is not currently a requirement to register the ACTIVE trial under the European Clinical Trials Directive (2001/20/EC).

6.2. Collagen membrane

The collagen membrane used to seal the chondral defect in ACI must have CE Mark certification for that purpose. It is not a requirement to register trials of CE marked products with the Medical Devices Agency.

6.3. Training requirements

6.3.1. Surgeons

All recruiting surgeons will be experienced in performing knee surgery and will be required to confirm that they have previous experience of each of the techniques they may use. As the trial is a randomised design, patients may be allocated to either the ACI arm or to the alternative treatments arm. Surgeons must therefore have previous experience of ACI (with periosteum and with collagen membrane). In the alternative arm, the surgeon will select the appropriate treatment option. This must be an option with which the surgeon has had previous experience.

To participate in the ACTIVE trial the minimum experience for each procedure before recruitment to the trial is regarded as one of the following

- At least 1 procedure supervised by an already experienced surgeon
- 5 unsupervised procedures

If necessary, surgeons can gain experience of ACI under the supervision of the Chief Investigator, Professor Richardson. In addition, for ACI, each surgeon must have had training in the use of a collagen membrane. This training can be provided by Geistlich and is a requirement for all surgeons using the Geistlich membrane. Geistlich will provide special workshops for surgeons participating in the ACTIVE trial. Training in the MACI® technique will be organised by Genzyme Biosurgery. Training in Chondron™ will be organised at the RNOH, Stanmore.

The Department of Health Interventional Procedures Programme (November 2003) requires that any surgeon undertaking a new procedure for the first time must seek approval from the local Clinical Governance Committee. As surgeons participating in ACTIVE will have used all the procedures before, this will not be necessary. Approval would not be necessary in any event when a procedure is used within a protocol approved by the REC.

6.3.2. Local study coordinators

Each site's Principal Investigator should identify a local coordinator to take responsibility for obtaining patient consent, organising blood tests, randomisation of patients and scheduling the allocated procedure. They will continue to work with the trial manager throughout the trial. Training days for local coordinators will be arranged before recruitment starts at each site.

6.3.3. Independent assessors

Each site should identify a suitable person (e.g. a physiotherapist) who will be trained centrally in outcome assessment. To remain blinded this person should not be involved in the usual clinical care of the patient. Since this person will need to obtain the pre-operative functional knee scores and quality of life indicators, this training will also take place prior to recruitment.

7. OUTCOME MEASURES

7.1. Primary Outcome Measures

Joint primary outcomes will be employed:

i) The time from randomisation until cessation of benefit of treatment (in months) measured once all patients have completed three years follow-up up to and including a maximum of five years follow-up. Cessation of benefit of treatment will be assessed using a combination of self-reported functional knee scores and functional assessments by a blinded independent assessor (further details on the calculation are given in the Statistical Analysis Plan);

A cessation of benefit form (Appendix 5) will be completed by a trained, blinded, independent assessor. Patients will be advised that treatment allocation must not be revealed and that both legs should be covered.

Cessation of benefit forms will normally be completed at the pre-specified follow-up points. In addition, if the patient is due to receive a further procedure on the previously treated knee, the trial office should be contacted, and a cessation of benefit form filled out to determine knee status prior to further procedure.

Using the cessation of benefit form the assessor will confirm:

- the current independently assessed Lysholm form is complete
- the patient self-assessed Lysholm knee questionnaire is complete
- whether the patient's knee has improved or not since pre-op in terms of swelling, range of motion and pain.

The form will then be returned to the Trial Office.

The 3 criteria to be used for assessment of no benefit or cessation of benefit are:

- No meaningful gain in independently assessed Lysholm knee score compared with pre-operative score (less than four points improvement from baseline score)
- No meaningful gain in patient's self–assessed Lysholm knee score compared with pre-operative Lysholm score (less than four points improvement from baseline score)
- Overall knee status judged by the assessor as not improved from pre-operative condition.

Cessation of benefit is defined as 2 out of the 3 criteria being met. Four points was selected as a cut-off here as it is only considered to be 'minimal improvement: 0.2SD (23). The SD is assumed to be 20 points, i.e. 0.2SD=4 points.

Patients are given 12 months to see if their treatment was successful. If no benefit has been seen up to and including the 12 month time-point then the failure time will be taken as day one. If the patient has been judged to have ceased benefit prior to 12 months (3/6 months) these will be ignored provided some benefit has been seen at 12 months.

Additional procedures (recorded in the additional procedure form) will be incorporated into the above analysis using the following rules:

- If the need for an additional procedure was decided upon at a scheduled assessment time then outcomes will be determined as per the above and no extra calculation will be required.
- If the need for an additional procedure was decided upon outside of a scheduled assessment time and extra assessment data is available then this will be incorporated into the overall calculation using the date when was it decided an additional procedure was needed.
- In the cases where an additional procedure was decided upon outside of a scheduled assessment time and the standard assessment data are not available then cessation of benefit will be determined by a third-party independent assessment blinded to the treatment group. Output will take the form of ceased benefit'/'not ceased benefit' and data will be incorporated into the overall calculation using the date when was it decided an additional procedure was needed.

ii) A knee specific measure, the Lysholm score (Appendix 7 & 8), as completed by the patient (0=worst outcome, 100=best outcome) including responses at one, two, three, four and five years follow-up. A two-stage approach will be utilised here: if there is evidence of a changing effect over time (see the Statistical Analysis Plan for how this will be determined), five years will be considered the outcome time of most interest with estimates at the other times considered to be secondary outcomes. If no such evidence exists, an estimate over all five time points will be produced (also see section 10.7 for how this will be calculated). The rationale for choosing five years is that if any benefit of ACI over standard treatment exists is it likely to be in the longer term.

The Lysholm Knee Score (24) is an eight-item questionnaire of knee function. Scoring is on a 100-point scale with 25 points for pain, 25 points for stability, 15 points for locking, 10 points each for swelling and stair climbing and 5 points each for limping, squatting and support. The Lysholm score has been validated and is widely used (25).

7.2. Secondary Outcome Measures:

7.2.1. Functional knee scores

The Lysholm (Appendix 7 & 8) will also be completed by the by blinded observer.

The patient-assessed IKDC (Appendix 9) and Cincinnati Sports Activity rating (Appendix 10) will be used. The IKDC form incorporates a demographic form, current health assessment form, subjective knee evaluation form, knee history form, surgical documentation form, and knee examination form. The IKDC subjective knee evaluation form will be used in the ACTIVE study. This score was designed to detect changes in patients with a variety of knee conditions including articular cartilage lesions as well as meniscal and ligament injuries. It has been validated as a knee-specific score for patients with a wide variety of knee problems (26). It is divided into three parts relating to symptoms, function, and sports activity. Scoring responses from the questionnaire are transformed to a scale with range 0-100 points using a standard formula according to item-response theory. The Cincinnati knee rating

system was first published in 1983 (27, 28). In all it has 11 components, including a subjective clinician's rating, patient's perception, symptom rating, Sports Activity Scale, Activities of Daily Living Function scales, Sports Function scales, Occupational rating scale, overall rating scheme, physical examination, laxity of the knee on instrumented testing and radiographic evidence of degenerative joint disease. Again, the Cincinnati system is in wide usage and has been validated in two studies (1, 25). For the purposes of ACTIVE, the Sports Activity Scale, Activities of Daily Living Function scales and Sports Function scales will be used. There is quite an overlap between these forms. This is because these questionnaires have been used in other studies with which comparison will be made. Each of the forms needs to be completed IN FULL at each scheduled time.

7.2.2. Quality of life indicator-EQ5D

Knee injuries can have a significant impact on a patient's physical function and quality of life and this may be reflected in a general health score. General health measures also assess psychological health components and make comparisons that can be used for health economic analysis. The cost-benefit evaluation of ACI is increasingly important. EQ5D (29) (Appendix 11) is a general health assessment tool that gives a rating based on five questions and a health status based on a visual analogue scale. This form is very simple and quick to administer and is in wide usage. No licence is required for non-commercial research.

7.2.3. Resource Usage

Use of health service resources and privately incurred costs will be recorded at all the intervals (see schedule and schema) using a structured Resource Usage questionnaire (Appendix 12). This will enable health economic evaluation (see 10.1)

8. DATA COLLECTION

Functional knee scores, Quality of Life indicators and resource usage data, will be collected both at clinic visits and by post. To maintain contact with patients over the 10 year follow-up and to avoid sending questionnaires to deceased patients the Trial Manager/local study coordinators will use the NHS Summary Care Record to trace patients who may have moved to a new address, and to identify any patients who have died. A change of contact details form will also be sent with each postal questionnaire.

8.1. Treatment Record Form

All surgical data will be collected on the Treatment Record Form (appendix 13). This form will be considered source data and must be signed by the investigator and filed with the participant's medical notes. A copy of the form must be sent to the central trial office.

8.2. Scheduled Clinic visits

Clinic visits will take place pre-operatively and at 2 months, 6 months, 12 months, and years 3, 5 and 10 post-operatively. These visits will be timed to coincide with out-patient appointments as much as possible to minimise extra burden on trial

participants. Where the visit is purely for trial purposes, travel expenses will be reimbursed.

Trial participants will be asked to complete Functional knee scores, Quality of Life indicators and resource usage questionnaires at each visit. In addition, a `blinded' assessor, usually a physiotherapist, who has no knowledge of the treatment allocation, will conduct a semi-structured interview and an assessment of swelling, pain and range of movement with the trial participant in order to complete the cessation of treatment benefit form. Patients will be advised that treatment allocation must not be revealed and that both legs should be covered.

Following completion of the assessment and questionnaires the assessor will input the data into the ACTIVE trial database, and send copies of the completed questionnaires to the central trial office.

It should be noted that longer term analyses, after the primary analysis (up to five years follow-up) has been published, will not include any independent assessments. The study will continue with patient reported outcomes only. In practice this means that the 10 year clinic visits will not be necessary and outcome measures will be collected by post. A revised Patient Information Leaflet will be sent by the coordinating centre to all participants to advise of this change (Appendices 17 & 18). It is not necessary to receive written informed consent from participants regarding this change.

8.3. Postal Questionnaires

Questionnaires will be posted to trial participants at years 2, 4 and 6-9. These will be administered and collected by the central trial office. After the primary analysis (up to five years follow-up) has been published, Outcome measures will also be collected by post at the 10 year time-point (see section 8.2 above).

8.4. Unscheduled clinic visits

Where an additional surgical procedure to the trial knee is deemed necessary by the orthopaedic surgeon, it is important that knee status is collected prior to the procedure. This will be done at an additional assessment, preferably to coincide with the routine pre-operative assessment appointment. The additional assessment collects all outcome data as in scheduled assessments, except for resource usage. An additional assessment must be carried out if a scheduled assessment has not taken place since the decision was made for further surgery.

In the cases where an additional procedure was decided upon outside of a scheduled assessment time and the standard assessment (cessation of benefit form/Lysholm patient/Lysholm assessor) data are not available then cessation of benefit will be determined by a third-party independent assessment blinded to the treatment group.

8.5. Additional surgical procedures

An additional surgical procedure form (appendix 6) should be completed and signed by the orthopaedic surgeon as soon as possible after the procedure itself and a judgement made on the repair of the original defect and any new defects treated. This form must be returned to the central trial office.

8.6. Participant retention

A participant newsletter will be sent from the central trial office on an annual basis to maintain levels of interest in the trial and encourage continued participation.

However, It is anticipated that there will be a reduction in the number of assessments/questionnaires that are completed and returned as the length of time from treatment increases. In order to encourage completion of follow-up assessments by trial subjects and reduce this potential loss of long-term follow-up data, all sets of completed questionnaires will be entered into a twice-yearly prize draw for a £25 high street shopping voucher. A covering letter will be sent with all postal questionnaires to explain the conditions of the draw (appendix 14). The draw will be administered by the central trial office and winners reported in the annual participant newsletter (with the participant's permission).

Where difficulty in maintaining contact and/or booking follow-up visits with a trial participant is experienced, the local coordinator/trial manager will send a letter to encourage continued participation but also offer the option to withdraw from the trial if desired. (see appendix 15)

A participant knee diary is provided to all participants on an annual basis to help with completion of the questionnaires (appendix 16).

9. STATISTICAL ANALYSIS

9.1. Sample Size and Power Considerations

The sample size for this trial has been estimated based on data that suggest that approximately 40% of patients treated with conventional therapies require an additional surgical intervention within 5 years (3). Since patients requiring a further procedure are almost certain to have suffered a cessation of benefit as defined in Section 6, event rates in this trial are likely to be slightly higher. The original proposed sample size of 660 would enable the detection of a proportional reduction of 30% (40% to 28%) in the failure rate with 90% power at p=0.05 (30). A smaller sample size of 480 would provide 80% power to detect the same 30% reduction in numbers requiring an additional procedure. This size of sample would also provide 90% power (p=0.05) to detect a small to moderate effect size[2] of 0.3 of a standard deviation in patient Lysholm score at any one time point.

9.2. Data Analysis

A separate Statistical Analysis Plan will be produced and will provide a more detailed description of the planned statistical analyses. A brief outline of these analyses is given below. In general, the primary comparison groups will be composed of those treated with ACI versus those treated with standard treatment. All primary analyses will be based on the intention to treat principle, with all patients analysed in the arms to which they were allocated irrespective of compliance with the randomised allocated treatment, and all patients will be included in the analyses. For all major outcome measures, summary statistics and differences between groups will be presented, with confidence intervals and

p-values from two-sided tests also given. Outcomes will be unadjusted in the first instance, however adjustment for the minimisation variables listed in section 4.2 will be performed as a sensitivity analysis. A Bonferonni correction will be applied to the joint primary outcome measures (p-values multiplied by 2) to allow conventional interpretation of statistical significance at the 5% level.

9.2.1. Joint primary outcome analysis

i) Cessation of treatment benefit will be analysed using a Cox proportional hazard model. A chi-squared test will be used to determine statistical significance of the treatment group parameter in the model. Hazard ratios and a 95% confidence interval will be generated. Median survival time and interquartile range by group will also be presented. Kaplan-Meier curves by group will be constructed for visual presentation.

ii) Patient reported Lysholm scores will be analysed using a mixed regression model allowing for the repeated measures structure of the data. Baseline score will be included in the model. Interaction over time will examined and if significant ($p<0.05$) the difference between groups at five years will be considered the main outcome of interest. Otherwise a constant treatment effect over all of the assessment times will be assumed. Difference between groups and a 95% confidence interval will be generated from the model.

9.2.2. Secondary outcomes analysis

Other questionnaire scores will be analysed as per the primary outcome. For other binary outcomes, a generalised estimating equation model will be employed allowing for the repeated measures structure of the data. 99% confidence intervals will be used for these other outcomes with statistical significance considered to be at the 1% level.

9.2.3 Missing data and other sensitivity analysis

Every attempt will be made to collect full follow-up data. In particular, participants will continue to be followed-up even after any protocol treatment deviation or violation. It is thus anticipated that missing data will be minimal. However, missing data presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. For the analysis of time to cessation of benefit the primary methods of analysis proposed naturally allow for early drop-out (i.e. by censoring), however this does not take into account the fact that this outcome is composed of three separate outcomes (self-reported Lysholm knee scores and functional assessments by a blinded independent assessor), which may in turn be missing. The proposal here is for sensitivity analysis is to simulate the missing responses of these three components using a multiple imputation approach which will then feed into the broader time to cessation of benefit analysis. A similar sensitivity analysis will be performed for patient Lysholm scores. ‘Per protocol’ analyses for the joint primary outcomes will also be carried out to explore the potential effect of any cross-over. The effect of classifying any additional procedure as a ‘failure’ in the cessation of benefit analysis will be explored. The effect of additional procedures on patient reported Lysholm scores will also be investigated by assuming a carried forward (pre-intervention) score for those undergoing an additional procedure that was deemed to represent a failure of treatment (as defined earlier).

9.2.4 Subgroup analyses

Further details on the variables to be used for planned subgroup analyses will be given in the SAP. The effects of subgroups will be examined by adding a subgroup by treatment group interaction parameters to the linear and PH models. Statistical significance of the interaction parameters will be examined.

9.2.5 Planned final analyses

The primary analysis for the study will occur once all participants have completed the three year follow-up assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include any data already collected up to and including five years follow-up but no further. Timing of publication of longer term data will be discussed and agreed with the DMC after the main analysis has been published.

9.3. Data Monitoring & Ethics Committee

During the recruitment period interim analyses of major endpoints and safety data will be supplied annually (or more frequently if requested) in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies and any other analyses that the committee may request. The DMEC will advise the chair of the ACTIVE Trial Steering Committee (TSC) if, in their view, the randomised comparison in ACTIVE has provided both:

- "proof beyond reasonable doubt"[1] that for all, or for some, types of patient ACTIVE is definitely indicated or definitely contraindicated in terms of a net difference in time to cessation of benefit
- evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

Unless this happens, however, the Steering Committee, the collaborators and all of the central Trial staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

10. SAFETY

ACI is a well-tolerated procedure, and side-effects of treatment are expected to be rare, but collaborators should notify the trial office immediately of any serious unexpected adverse experiences believed to be due to any of the trial treatments by telephoning the study office and subsequently by completion of the Serious Adverse Events Form.

For the purposes of the ACTIVE trial a serious adverse event is an adverse event that occurs within one year of the end of treatment for the affected knee and is either:

[1] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations ($p \approx 0.002$) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the trial prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

(a) Deep vein thrombosis, a fall causing injury, infection to the knee joint

(b) results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

(c) An important medical event that, based on appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All Serious Adverse Events should be followed until resolved.

All serious adverse events should be assessed for causality and expectedness by the principle investigator as per the definitions below:

10.1. Assessment of Causality

Unrelated There is no evidence of any causal relationship

Unlikely There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible* There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable* There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely* There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

If the AE is serious and unexpected, the possible, probable and definitely related should be notified to the MHRA, the relevant REC and the Sponsor as SUSARS.

10.2. Assessment of expectedness

If the event is judged to be related (suspected), an assessment of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the investigator brochure.

10.3. Timeframes for reporting

The Serious Adverse Event Initial Report form should be completed and faxed to the central trial office within 24 hours of the principle investigator becoming aware of the event. Any additional information should be sent as soon as it becomes available on the Follow-up form

The CI must report all suspected (related) and unexpected serious adverse events to the Research Ethics Committee as soon as possible, but no later than **15 calendar days** after the CI has first knowledge of the event. Further relevant information should be given as soon as possible.

The DMEC will consider data from interim analyses, and any additional safety issues for the trial and will recommend to the TSC if the trial should be stopped for any safety reasons.

11. HEALTH ECONOMICS

Collection and analysis of data relating to economic evaluation will be supervised by Professor Marilyn James at the University of Nottingham.

11.1. Costs

Health economic evaluation will be from a societal perspective with both public sector and private cost data collected. Private costs will include days off work as well as any privately financed health care related to the knee. Health service costs will include any adverse events and treatments due to knee damage. As the trial will be multi-centred, unit costs specific to each centre will be collected for the major cost items including type of ACI (which may vary with supplier). Unit costs will also be collected for alternative conventional treatments, and main other knee related treatments that patients may require over the period of the trial.

11.2. Cost effectiveness analysis

Health economic analysis will use EQ5D (29) to estimate cost per Quality Adjusted Life Year (QALY). Cost effectiveness will be assessed both in terms of cost per QALY and per year free of further surgery. In addition ICERs (incremental cost effectiveness ratios) will be determined from usual care to ACI or MACI. Cost Effectiveness Acceptability Curves will be plotted for each of the options.

11.3. Modelling

Modelling will be required to combine trial and non-trial data, and for sensitivity analysis exploring the implications of a range of assumptions on the results. In addition, modelling will explore issues of patient drop out and censoring of data.

12. ORGANISATION

The **Host Institution** for the ACTIVE trial is Keele University. The Medical Research Council (MRC) is the funder and Keele University is the Sponsor. Keele University is accountable to the MRC for the conduct of the research and adherence to the principles of the Research Governance Framework.

The **Chief Investigator** is Mr Andrew Roberts. **Co-investigators** are Professor Richard Gray, Professor Marilyn James and Professor George Bentley.

The Chief Investigator has nominated a **Trial Steering Committee** (TSC) and a **Data Monitoring and Ethics Committee** (DMEC) and these have been approved by the MRC (see inside cover).

12.1. Ethical approval

The ACTIVE protocol has been approved by the TSC and also by the Multicentre Research Ethics Committee (MREC). Before recruitment at any site can begin, the Local Research Ethics (LREC) Committee must give `Locality' approval and local R&D management approval must be obtained.

12.2. Trial Manager

The Trial Manager is Dr Johanna Wales (full time during the recruitment phase, then decreasing) who will set up and coordinate collaborating sites, support patient recruitment, be responsible for budget management, and for the collection and reporting of outcome data.

12.3. Local organisation

Each collaborating site will formally identify a local **Principal Investigator** who will take responsibility for local conduct of the study in compliance with the Research Governance Framework and for obtaining LREC and local R&D management approval.

Keele University will put in place an agreement with each of the Collaborating sites setting out the requirements and responsibilities.

As soon as LREC and local R&D management approval have been confirmed, and an agreement is in place, the Trial Manager will visit the site to provide staff training and the ACTIVE trial materials. Randomisation can then begin.

Because of the many possible treatment allocations in this trial, the task of identifying eligible patients and fully informing the patient prior to obtaining consent should be with the recruiting surgeon, supported by the local co-ordinator.

12.4. Local study co-ordinators

Financial support will be provided to each collaborating site for assistance with recruitment. This will be pro-rata dependent on patient numbers and will be part of the collaborative agreement which the University of Keele will make with each recruiting centre. Collaborating sites are advised to identify appropriate personnel as local study coordinators. This person will obtain and document consent, organise blood tests, randomise patients and subsequently schedule the allocated procedure.

12.5. Independent (blinded) outcome assessors

In order to minimise the potential for bias, a pre-operative assessment and some of the outcomes will be assessed by a `blinded' assessor who has no knowledge of the treatment allocation and must not be told by the patient, study co-ordinator or surgeon. The patient's leg will be covered with tubigrip. The assessor should have no part in the normal care of the patient. The schedule of blinded assessments is displayed on page 18. Assessments are mainly in the form of questionnaires (functional knee scores, Quality of Life measures and resource usage) and functional assessments although a simple examination to detect swelling of the knee will be required. It is envisaged that the assessment could be carried out by a physiotherapist and a `per-event' payment will be available.

Training will be provided centrally early in the study. On-going support will be available from the Trial Manager.

12.6. Research costs

The Medical Research Council funds the research costs of the study only. Research costs include the trial manager, central statistics and health economics evaluation, collecting self-assessed outcome data from patients by post, training for local study coordinators and independent assessors and the costs of the TSC and DMEC. It also provides some support for the input of time of local study coordinators and for the independent outcome assessors, depending on recruitment. This will be part of the individual agreements between Keele University and each collaborating site.

12.7. Treatment costs

The costs of the treatments in any trial fall within normal contracting arrangements. Because autologous chondrocyte implantation (ACI) is more expensive than the standard treatments, the Department of Health is supporting the *excess treatment* costs through a Central Subvention fund. Parallel arrangements are in place for Scottish and Welsh patients through the Wales office of R&D and Scottish Executive Health. Each recruiting centre has been advised on how to access the Central Subvention fund in a letter from the Head of the NHS R&D Policy, Department of Health, October 2003.

12.8. Service Support costs

There are additional costs consequent to the trial that fall into this category. These are the additional time required in an outpatient clinic to inform and recruit patients, the costs of pre-randomisation blood tests for those patients who would not normally need tests and 4 outpatient appointments over 10 years for each patient, additional to normal practice. The level of the service support costs has been agreed by the Department of Health. In line with the Concordat that exists between the Medical Research Council and the NHS, organisations are expected to meet these costs from their NHS R&D Budget. Organisations not in receipt of NHS R&D funding, or for whom the service support costs present difficulty should contact the Department of Health for advice about the *ad hoc* arrangements. From 2008 this funding can be claimed through the UKCRN (portfolio ref. 2432).

12.9. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participation in the study. ACTIVE is not an industry-sponsored trial and so ABPI guidelines on indemnity do not apply. Normal NHS indemnity liability arrangements for clinician-initiated research will apply in ACTIVE.

Geistlich Pharma has offered to supply Chondro-Gide® collagen membrane free of charge for recruited patients under a Material Transfer Agreement. Chondro-Gide® is a CE marked non-active implant, normally available for use in ACI. Geistlich Pharma has not been involved in the design or conduct of the trial in any way and will have no special access to data.

12.10. Publication

The ACTIVE trial is a long-term study with 10 year follow up. Given the scale of the project it is envisaged that a number of publications will be generated. The first principal analyses to be reported in peer-reviewed journals will be undertaken in year 5, or after 3 years follow-up.

The success of ACTIVE depends entirely on full collaboration of a large number of people. Depending on the publication policy of the journal(s) any publication will either be in the name of the study i.e. ACTIVE with all collaborating leads identified or with an authorship including all those who have collaborated in the study.

It is essential that the trial protocol is followed and that no additional investigations conflict with either the treatments or the outcome measures. For this reason it is requested that any proposals for additional studies related to the trial be referred to the Trial Steering Committee for consideration. Any intention to publish a case report or case series from an individual site must first be advised to the Trial manager for approval by the Trial Steering Committee and this will be part of the agreement between each collaborating site and the Host Institution.

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14. SCHEDULE OF ASSESSMENTS

	1 Pre-op Clinic	2 2/3 months Clinic	3 6 months Clinic	4 1 year Clinic	5 2 year by post	6 3 years Clinic	7 4 years by post	8 5 years Clinic	9 6 years by post	10 7 years by post	11 8 years by post	12 9 years by post	13 10 years Clinic
Assessment window	**n/a**	**8-16 weeks**	**21 – 34 weeks**	**10-15 months**	**1.5 – 2.5 years**	**2.5 – 3.5 years**	**3.5 – 4.5 years**	**4.5 – 5.5 years**	**5.5 – 6.5 years**	**6.5 – 7.5 years**	**7.5 – 8.5 years**	**8.5 – 9.5 years**	**9.5 – 10.5 years**
Blinded Observer Lysholm	X	X	X	X		X		X					X*
Blinded Observer Cessation of benefit				X		X		X					X*
Patient Lysholm	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient IKDC	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient EQ5D	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Cincinnati	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Resource usage		X	X	X	X	X	X	X	X	X	X	X	X

* Prior to publication of primary outcome measure only

CTIVE SCHEMA

ELIGIBILITY

- Symptomatic chondral/osteochondral defect(s) on the medial or lateral femoral condyle or trochlea suitable for either ACI or one of the existing conventional treatments (debridement, abrasion, drilling, microfracture, AMIC, mosaicplasty)
- Not more than 2 defects, not kissing and total area not greater than 12 cm^2
- Surgical treatment/washout for the same defect, carried out at least 6 months previously, that has failed
- No concurrent total meniscectomy/osteotomy or untreated malalignment of patella
- No generalised osteoarthritis, inflammatory condition or history of mesenchymal tumours
- Likely to comply with appropriate physiotherapy
- HIV, Hepatitis B & C, Syphilis, HTLV I & II negative (or tests as required by the cell supplier)
- Patient not in clinical trial involving the knee, currently or in last 6 months

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RANDOMISATION

- Obtain patient's written informed consent
- Serology: all tests as required by cell provider completed and negative
- Specify ACI or MACI options (which may include a sub-randomisation as listed below)
- Decide treatment in the event patient is randomised to `alternative' arm of trial
- Ring randomisation service and answer all questions on Registration Form
- Eligible patients will be randomised

Randomise

ACI or MACI (according to choice)

- With periosteum or
- With collagen membrane or
- sub-randomised to periosteum vs. collagen

- MACI or
- Sub-randomised to MACI vs. Chondron

ALTERNATIVE

- Debridement
- Drilling
- Microfracture
- AMIC
- Mosaicplasty
- Bone graft

PRE-OPERATIVE ASSESSMENT

(i) Independent observer
Semi-structured interview
Physical/functional assessment
Lysholm knee score

(ii) Patient Self-assessment
Lysholm knee score
Cincinnati score
EQ5D
IKDC

TREATMENT

When the above assessment has been completed and confirmed, the ACTIVE treatment allocation will be issued. Treatment will be completed as soon as possible

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FOLLOW UP

(i) Clinic assessments at 2/3 & 6 months & 1, 3, 5 & 10 years post-op (N.B. 10 year follow-up will not include Independent observer assessments after the primary outcome data has been published)

(i) Independent (blinded) observer
Semi-structured interview
Physical/functional assessment
Lysholm knee score
Cessation of benefit

(ii) Patient self-assessment
Lysholm knee score
Cincinnati score
EQ5D
IKDC
Resource usage

(ii) Patient self-assessment postal questionnaires at 2, 4, 6, 7, 8, & 9 years post-op
Lysholm knee score
Cincinnati score
EQ5D
IKDC
Resource usage
