AUTOLOGOUS CHONDROCYTE TRANSPLANTATION / IMPLANTATION VERSUS EXISTING TREATMENTS
ISCRCTN 48911177

PROTOCOL

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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:
  1. ACI (surgeon can choose either ACI or MACI or a sub-randomisation between two types of matrix-assisted ACI: MACI and Chondron) or
  2. 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 primary outcome measure will be time to cessation of benefit of treatment.

- Secondary outcomes will be functional knee scores (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.
1. BACKGROUND TO TRIAL

1.1. 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-trabeular 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 4cm²; (5) but this procedure is not recommended for larger lesions.

1.2. 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 - Autologous Chondrocyte Transplantation / Implantation Versus Existing standard treatments.

1.3. 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 12 months post-treatment. A detailed health economics analysis will take into account the cost of different treatments allocated.

2. 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.

2.1. 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.

2.2. 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.

3. TRIAL RANDOMISATION

3.1. 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 cm² 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.

3.2. 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 Coordinator 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.
4. SURGICAL TECHNIQUES

4.1. 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).

4.2. 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.

4.3. 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.

4.4 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.

4.5. 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.

4.6. 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 (21) 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 inwards to 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.

4.7. 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.

5. REGULATIONS AND TRAINING
5.1. 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).

5.2. 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.

5.3 Training requirements
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.

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.

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.

6. OUTCOME MEASURES
6.1. Data collection
Functional knee scores, Quality of Life indicators and resource usage data, will be collected pre-operatively, then at 2-3 months, 6 months, 1, 3, 5, and 10 years in clinic (by interview and self assessed) and annually in intervening years by patient using post or electronic means (see Schema, p. 18). 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 National Strategic Tracing System to trace patients who may have moved to a new address, and to identify any patients who have died.

6.2. Primary: Cessation of benefit of treatment
A cessation of benefit form (Appendix 2) 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 gain in independently assessed Lysholm knee score compared with pre-operative score
- No gain in patient’s self-assessed Lysholm knee score compared with pre-operative Lysholm 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 and will be identified by the Trial Office.

6.3. Secondary: Functional knee score
A knee specific measure, the Lysholm (Appendix 3 & 4) assessed both by blinded observer and by patients and the patient-assessed IKDC (Appendix 5) and Cincinnati Sports Activity rating (Appendix 6) will be used.

The Lysholm Knee Score (23) 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 (24). However, the scale was originally designed to assess patients following knee ligament surgery with a special emphasis on symptoms of giving way, and this is reflected in the weighted scoring system.

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 (25). 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 (26, 27). 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, 24). 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.

6.4 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 (28) (Appendix 7) 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.

6.5. 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 8). This will enable health economic evaluation (see 9.1). 

7. STATISTICAL ANALYSIS
7.1 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 (29). A smaller sample size of 480 would provide 80% power to detect the same 30% reduction in numbers requiring an additional procedure. Should event rates be higher, then the proportional reduction that can be detected will be correspondingly smaller (e.g. 50% to 37.5%, a proportional reduction of one quarter). The proposed reduction is equivalent to an improvement in median time to failure of around 2 years, representing a cost per failure-free year of approximately £8,000. The minimum sample size of 480 patients would also provide 90% power to detect a small to moderate effect size of 0.3 of a standard deviation in the continuous outcome variables (e.g. Lysholm knee score) at p=0.05.

7.2 Data Analysis
The same methods of analysis will be used for the main ACI versus standard treatment, and for the sub-randomisation between types of membrane and types of matrix-assisted ACI. The primary endpoint is time to the cessation of treatment benefit as defined in Section 6. Data for this endpoint will come from the prespecified assessment time-points, as well as the additional assessments undertaken when a patient presents for a further procedure. Analysis of this endpoint will be by means of standard log-rank methods and stratified analyses presented using odds ratio plots (30). If, during the first year following surgery, the patient would have been deemed to have derived no benefit from surgery at all assessment points (using this endpoint) then the procedure is deemed to have failed, and the patient will be analysed as suffering an event on day 1. For the continuous outcome measures, repeated measures analyses will be performed on the change from the baseline scores, using standard multilevel mixed modelling techniques using SAS PROC MIXED. Such analyses have the
advantages of being able to combine results from different time-points to maximise power, and also to investigate the precise form of any benefit (whether, for example, any treatment benefit, should one exist, increases or decreases with time). Multilevel modelling also allows for suitably stratified analyses to be performed.

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. For this reason, the only prespecified subgroup analyses are those defined by the stratification variables (intended control and cell-grafting treatment options, size of chondral defect, age, pre-operative functional knee score, femoral or trochlea/patella defect), as well as period of study, to investigate any potential learning effects. In addition, to investigate possible differences in the effectiveness of ACI between centres, analyses stratified by centre will be performed.

7.3 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" 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.

8. 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 (Appendix 9).

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.

9. HEALTH ECONOMICS
Collection and analysis of data relating to economic evaluation will be supervised by Professor Marilyn James at the Centre for Public, Health Liverpool John Moores University.

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1 Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations (p ≈ 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.
9.1. 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.

9.2. Cost effectiveness analysis
Health economic analysis will use EQ5D (28) 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.

9.3. 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.

10. 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 Professor James Richardson. 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).

10.1. 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.

10.2. Trial Manager
The Trial Manager is Dr Heather Smith (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.

10.3. 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.

10.4. 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.

10.5. Randomisation
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 10). At this stage the surgeon will complete Parts A&B of the Patient Entry Form (Appendix 1) 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 11) and the patient’s GP will be informed (Appendix 12). The study coordinator will then complete all questions in Part C of the Patient Entry Form (Appendix 1), and submit all details using the online randomisation system or by phoning Birmingham Clinical Trials Unit. The allocated procedure will then be advised, and the treatment scheduled according to local practice. 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. When treatment has been completed the Treatment Record Form (Appendix 13) will be completed by the surgeon and entered onto the database by the co-ordinator.

10.6. 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.

10.7. 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.

10.8. 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.

10.9. 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).

10.10. 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.

10.11. 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.
11. REFERENCES


### SCHEDULE OF ASSESSMENTS

<table>
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<tr>
<th></th>
<th>1 Pre-op Clinic</th>
<th>2 2/3 months Clinic</th>
<th>3 6 months Clinic</th>
<th>4 1 year Clinic</th>
<th>5 2 year by post</th>
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<th>7 4 years by post</th>
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</tbody>
</table>
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 cm²
- 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

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

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

Follow up

(i) Clinic assessments at 2/3 & 6 months & 1, 3, 5 & 10 years post-op

(ii) Patient self-assessment postal questionnaires at 2, 4, 6, 7, 8, & 9 years post-op
You will need to answer the questions on this form when randomising, either by phone on 0800 953 0274 (+44 (0) 121 687 2319 outside UK), or web randomisation on https://www.trials.bham.ac.uk/active

When patients are identified prior to randomisation, surgeon should complete parts A & B and pass form to local trial coordinator. At randomisation, local trial coordinator should check that parts A & B are complete and correct before randomising the patient.

## PART A: IDENTIFYING DETAILS

<table>
<thead>
<tr>
<th>Hospital Name</th>
<th>Responsible clinician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Surname</td>
<td>Given Name(s)</td>
</tr>
<tr>
<td>Patients’ Address</td>
<td></td>
</tr>
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</table>

Date of Birth (dd:mon: yyyy) | Sex: M ☐ F ☐ Tel. No. |

| Hospital number | N.H.S. Number |

## PART B: PATIENT’S MEDICAL DETAILS

| Affected Knee | Left ☐ Right ☐ Both (ineligible) ☐ |

Date of most recent procedure (dd:mon: yyyy) | Type: |

(n.b. randomisation must be at least 6 months post procedure)

Type of defect:  Medial femoral ☐ Trochlea ☐ Lateral femoral ☐ patella ☐ Predicted size ........... cm²

### PRE-RANDOMISATION ELIGIBILITY CHECKLIST

**If OCD, predicted depth of bone ........ mm**

- Generalised OA, inflammatory condition or history of mesenchymal tumours? ☐ No ☐ Yes (ineligible)
- Untreated malalignment of patella or unstable knee? ☐ No ☐ Yes (ineligible)
- Concurrent total meniscectomy or osteotomy? ☐ No ☐ Yes (ineligible)

**Intended STANDARD treatment:** ☐ Debridement ☐ bone graft ☐ Drilling ☐ Microfracture ☐ Mosaicplasty ☐ AMIC

**Intended CELL-GRAFTING treatment:** ☐ ACI (membrane) ☐ ACI (periosteum) ☐ ACI (rand. periosteum /membrane) ☐ MACI ☐ MACI (rand. Chondron/MACI)

**Expected date of surgery (mon: yyyy)** ...:............ (NB Surgery must take place within 3 months of randomisation)

Please pass this form now to the local trial coordinator who will contact the patient at a later date.

When ready to randomise, coordinator should check parts A and B and complete the rest of the form.

(Pre-registered patients) Details in Parts A&B been checked and/or corrected? ☐ Yes ☐ No (ineligible)

If patient decides not to take part, record below the reasons (if known) and return this form to the trial office

## PART C: RANDOMISATION DETAILS

### BLOOD TEST RESULTS - if required prior to randomisation – check with cell company

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<td>Negative ☐</td>
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<td>Positive (ineligible)</td>
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<td>Negative ☐</td>
</tr>
</tbody>
</table>

Has the patient given written informed consent? ☐ Yes ☐ No (ineligible)

Have all pre-randomisation assessments been completed? ☐ Yes ☐ No (ineligible)

**PLEASE HAVE THE PATIENT-RATED INDIVIDUAL ITEM LYSHOLM SCORES TO HAND WHEN RANDOMISING**

### TREATMENT ALLOCATION

**ACTIVE Trial number**

| ☐ ACI (periosteum) | ☐ ACI (membrane) | ☐ MACI | ☐ Chondron | ☐ Debridement | ☐ Bone graft | ☐ Drilling | ☐ Microfracture | ☐ AMIC | ☐ Mosaicplasty |

Please use the patient’s trial number on all correspondence / forms sent to the trial office. Please fax or send a copy of the consent form to the ACTIVE trial office and arrange for baseline assessments to be entered onto the ACTIVE database or sent to the trial office.

Contact Person: ________________________________ Telephone: ________________________________

N.B. After randomisation, follow-up data will be requested, even if the allocated treatment is not given or the diagnosis is changed.

**ACTIVE Trial Office, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shopshire, SY10 7AG. Fax: 01691 404170**
This form is to be completed by the independent assessor who is blinded to treatment allocation. During the assessment patients are asked not to reveal their treatment allocation and both of their legs should be covered.

**Section A**

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
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</thead>
<tbody>
<tr>
<td>Has the treatment option been revealed to the assessor?</td>
<td>☐</td>
</tr>
<tr>
<td>Has there been an additional injury to the trial knee?</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Section B**

- Is the current independently assessed Lysholm form complete? Yes ☐
- Is the current patient self-assessed Lysholm form complete? Yes ☐

In the assessor’s view has the patient’s knee improved or not compared to pre-operatively? (e.g. swelling, range of motion, pain, functional performance, impact on quality of life)

*Please refer back to your assessment notes then delete one:*

- improved / not improved

Which treatment would you guess this patient had?

ACT ☐ or Alternative ☐ (please specify) ............................

Name of assessor ..................................................................................................................

Signed .................................................... (please sign)  Date ......... / ....... / .........

Date Completed ......... / ....... / .........

Date Entered ......... / ....... / .........

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.
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<tbody>
<tr>
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<tr>
<td></td>
<td>6</td>
<td>Constant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTABILITY</th>
<th>1</th>
<th>No giving way</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Rarely, during athletics or other severe exertion</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Frequently, during athletics or other severe exertion</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Occasionally, in daily activities</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Often, in daily activities</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>At every step</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOCKING</th>
<th>1</th>
<th>No locking and catching sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Catching sensation but not a locking sensation</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Locking occasionally</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Frequently</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Locked joint upon examination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SWELLING</th>
<th>1</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>On severe exertion</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>On ordinary exertion</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Constant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIMP</th>
<th>1</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Slight or periodical limp</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe and/or constant</td>
</tr>
</tbody>
</table>

PTO
**STAIR-CLIMBING**

1 □ No problems  
2 □ Slightly impaired  
3 □ One foot at a time  
4 □ Impossible because of knee

**SQUATTING**

1 □ No problems  
2 □ Slightly impaired  
3 □ Not beyond 90°  
4 □ Impossible because of knee

**SUPPORT**

1 □ None  
2 □ Cane or crutch  
3 □ Weight-bearing is impossible

Name of assessor  .................................................................  
Date Completed      ........ / ........ / ........

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This questionnaire has been designed to give information as to how your knee has affected your ability to manage in everyday life. Please answer every section and tick the box to the left of the statement that applies to you for your affected knee only. If more than one statement applies to you tick the one that most closely describes your situation.

### PAIN
1 □ I have no pain in my knee
2 □ I have intermittent pain in my knee during severe exertion
3 □ I have marked pain in my knee during severe exertion
4 □ I have marked pain in my knee on or after walking more than 2km
5 □ I have marked pain in my knee on or after walking less than 2km
6 □ My knee is in constant pain

### INSTABILITY
1 □ My knee never gives way
2 □ My knee rarely gives way during athletics or other severe exertion
3 □ My knee frequently gives way during athletics or other severe exertion
4 □ My knee occasionally gives way during daily activities
5 □ My knee often gives way during daily activities
6 □ My knee gives way with every step I take

### LOCKING
1 □ I experience no locking or catching sensation
2 □ I do experience a catching sensation but not a locking sensation
3 □ I occasionally have a locking sensation
4 □ I frequently have a locking sensation
5 □ I have a locked knee now

### SWELLING
1 □ My knee does not swell
2 □ My knee swells on severe exertion
3 □ My knee swells on ordinary exertion
4 □ My knee is constantly swollen

### LIMP
1 □ I have no limp
2 □ I have a slight limp or periodical limp
3 □ I have a severe and constant limp

PTO
### STAIR-CLIMBING

1. □ I have no problems climbing stairs because of my knee
2. □ My stair-climbing is slightly impaired because of my knee
3. □ I climb stairs one foot at a time because of my knee
4. □ Stair-climbing is impossible due to my knee

### SQUATTING

1. □ I have no problems squatting
2. □ My squatting is slightly impaired because of my knee
3. □ I can’t squat beyond 90°
4. □ Squatting is impossible because of my knee

### SUPPORT

1. □ I am not using any kind of support
2. □ I am using a stick or crutch
3. □ Weight-bearing is impossible for me due to my knee(s)

Has anything gone wrong with your knee (complications)? Please list below

Please answer the following question only after you have had your operation

1. □ I am extremely pleased with the operation – would recommend it
2. □ I am pleased with the operation
3. □ I am no different to before the operation
4. □ I am worse than before the operation
5. □ I am much worse than before the operation – wouldn’t recommend it

Thank-you for completing this questionnaire.

Please Insert the date when you completed this form ........ / ........ / ........ and return in the pre-paid envelope together with your other forms

For Assessor to complete:

Date Entered ........ / ........ / ........

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**SYMPTOMS**:
*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.*

1. **What is the highest level of activity that you can perform without significant knee pain?**
   1. ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
   2. ☐ Strenuous activities like heavy physical work, skiing or tennis
   3. ☐ Moderate activities like moderate physical work, running or jogging
   4. ☐ Light activities like walking, housework or yard work
   5. ☐ Unable to perform any of the above activities due to knee pain

2. **During the past 4 weeks, or since your injury, how often have you had pain?**
   - Never
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   - Constant

3. **If you have pain, how severe is it?**
   - No pain
   - Never
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   - Worst pain

4. **During the past 4 weeks, or since your injury, how stiff or swollen was your knee?**
   - Not at all
   - Very
   - Extremely

5. **What is the highest level of activity you can perform without significant swelling in your knee?**
   1. ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
   2. ☐ Strenuous activities like heavy physical work, skiing or tennis
   3. ☐ Moderate activities like moderate physical work, running or jogging
   4. ☐ Light activities like walking, housework or yard work
   5. ☐ Unable to perform any of the above activities due to knee pain

6. **During the past 4 weeks, or since your injury, did your knee lock or catch?**
   - Yes
   - No

7. **What is the highest level of activity you can perform without significant giving way in your knee?**
   1. ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
   2. ☐ Strenuous activities like heavy physical work, skiing or tennis
   3. ☐ Moderate activities like moderate physical work, running or jogging
   4. ☐ Light activities like walking, housework or yard work
   5. ☐ Unable to perform any of the above activities due to knee pain

**SPORTS ACTIVITIES:**

8. **What is the highest level of activity you can participate in on a regular basis?**
   1. ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
   2. ☐ Strenuous activities like heavy physical work, skiing or tennis

PTO
3  Moderate activities like moderate physical work, running or jogging
4  Light activities like walking, housework or yard work
5  Unable to perform any of the above activities due to knee pain

9. How does your knee affect your ability to:

<table>
<thead>
<tr>
<th>Activity</th>
<th>1 Not difficult at all</th>
<th>2 Minimally difficult</th>
<th>3 Moderately difficult</th>
<th>4 Extremely difficult</th>
<th>5 Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Go upstairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Go downstairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Kneel on the front of your knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Squat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Sit with your knee bent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Rise from a chair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Run straight ahead</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Jump and land on your involved leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Stop and start quickly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

A. FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform 0 1 2 3 4 5 6 7 8 9 10 No limitation in daily daily activities

B. CURRENT FUNCTION OF YOUR KNEE:

Cannot perform 0 1 2 3 4 5 6 7 8 9 10 No limitation in daily daily activities

Thank-you for completing this questionnaire

Please insert the date when you completed this form ........ / ........ / .......... and return in the pre-paid envelope together with your other forms

For trial staff to complete:

Date Entered ........ / ........ / ........

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Page 2 of 2
1. **Sports Activity Scale**

*Please tick one of the boxes below to indicate your current level of sports activity:*

**Level I**
- I take part 4-7 days a week in sports involving
  1. Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)
  2. Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)
  3. No running, twisting, jumping (e.g. cycling, swimming, rowing)

**Level II**
- I take part 1-3 days a week
  4. Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)
  5. Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)
  6. No running, twisting, jumping (e.g. cycling, swimming, rowing)

**Level III**
- I take part 1-3 times/month
  7. Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)
  8. Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)
  9. No running, twisting, jumping (e.g. cycling, swimming, rowing)

**Level IV**
- I do not take part in any sports
  10. I perform activities of daily living without problems
  11. I have moderate problems with activities of daily living
  12. I have severe problems with activities of daily living: on crutches, full disability

2. **Activities of Daily Living Function Scales**

I do the following:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>tick one box</td>
<td>tick one box</td>
<td>tick one box</td>
</tr>
<tr>
<td>1. normal, unlimited</td>
<td>1. normal, unlimited</td>
<td>1. normal, unlimited</td>
</tr>
<tr>
<td>2. some limitations</td>
<td>2. some limitations</td>
<td>2. some limitations</td>
</tr>
<tr>
<td>3. short distance only without support</td>
<td>3. only 11-30 steps possible</td>
<td>3. only 6-10 possible</td>
</tr>
<tr>
<td>4. need to use stick/crutcher even for short distances</td>
<td>4. only 1-10 steps possible</td>
<td>4. only 0-5 possible</td>
</tr>
</tbody>
</table>

PTO
3. Sports Function Scales

1. Straight running
   - tick one box
   - 1 □ fully competitive
   - 2 □ some limitations, guarding
   - 3 □ definite limitations, half speed
   - 4 □ not able to do

2. Jumping/landing on affected leg
   - tick one box
   - 1 □ fully competitive
   - 2 □ some limitations, guarding
   - 3 □ definite limitations, half speed
   - 4 □ not able to do

3. Hard twists/pivots
   - tick one box
   - 1 □ fully competitive
   - 2 □ some limitations, guarding
   - 3 □ definite limitations, half speed
   - 4 □ not able to do

Thank-you for completing this questionnaire

Please insert the date when you completed this form ........ / ........ / ........
and return in the pre-paid envelope together with your other forms

For trial staff to complete:

Date Entered ........ / ........ / ........

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By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

**MOBILITY**
- I have no problems walking about [ ]
- I have some problems in walking about [ ]
- I am confined to bed [ ]

**SELF-CARE**
- I have no problems with self-care [ ]
- I have some problems washing or dressing myself [ ]
- I am unable to wash or dress myself [ ]

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities [ ]
- I have some problems with performing my usual activities [ ]
- I am unable to perform my usual activities [ ]

**PAIN/DISCOMFORT**
- I have no pain or discomfort [ ]
- I have moderate pain or discomfort [ ]
- I have extreme pain or discomfort [ ]

**ANXIETY/DEPRESSION**
- I am not anxious or depressed [ ]
- I am moderately anxious or depressed [ ]
- I am extremely anxious or depressed [ ]
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Thank-you for completing this questionnaire.

Please insert the date when you completed this form

......... / ........ / .......... and return in the pre-paid envelope together with your other forms

© EuroQoL Group

For trial staff to complete:

Date Entered   ........ / ........ / ..........
This questionnaire aims to explore the costs involved in having a knee cartilage defect. You may like to refer to your knee diary so that you can answer all the questions as accurately as possible. The questions refer to the period since your knee surgery which should be approximately 2-3 months. You should not include the period while you were in hospital having your knee surgery for the ACTIVE trial. If you have difficulty with answering any of the questions please give the best answer you can. The information will be treated as confidential.

VISITS TO THE HOSPITAL
Q1 Since your trial surgery have you been to the hospital about your knee?
   Yes □ No □ (if “no” go to Q9)
Q2 If yes, have you had any additional surgery (e.g., an arthroscopy) on your knee or an injection for your knee since your trial surgery?
   Yes □ No □ (if “no” go to Q4)
If yes, please complete the details below:

<table>
<thead>
<tr>
<th>Type of procedure (please name/describe)</th>
<th>Did you stay overnight?</th>
<th>How many nights?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery 1</td>
<td>No □ Yes □</td>
<td></td>
</tr>
<tr>
<td>Surgery 2</td>
<td>No □ Yes □</td>
<td></td>
</tr>
<tr>
<td>Surgery 3</td>
<td>No □ Yes □</td>
<td></td>
</tr>
</tbody>
</table>

Q3 For any surgery you had, please indicate how it was paid for:

<table>
<thead>
<tr>
<th>Who paid for your treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery 1</td>
</tr>
<tr>
<td>NHS □ myself/relative □</td>
</tr>
<tr>
<td>insurance □ employer □</td>
</tr>
<tr>
<td>Surgery 2</td>
</tr>
<tr>
<td>NHS □ myself/relative □</td>
</tr>
<tr>
<td>insurance □ employer □</td>
</tr>
<tr>
<td>Surgery 3</td>
</tr>
<tr>
<td>NHS □ myself/relative □</td>
</tr>
<tr>
<td>insurance □ employer □</td>
</tr>
</tbody>
</table>

Q4 Since your trial surgery have you had your knee x-rayed or scanned?
   No □ Yes □ (If yes, please complete the details below)

<table>
<thead>
<tr>
<th>If yes, how many times?</th>
<th>Who paid for your treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-ray</td>
<td>NHS □ myself/relative □</td>
</tr>
<tr>
<td></td>
<td>insurance □ employer □</td>
</tr>
<tr>
<td>MRI scan</td>
<td>NHS □ myself/relative □</td>
</tr>
<tr>
<td></td>
<td>insurance □ employer □</td>
</tr>
</tbody>
</table>
Q5 Since your trial surgery have you seen an Orthopaedic Surgeon for an outpatient clinic appointment at a hospital because of your knee?

No □ Yes □ If yes, how many times? ____

Q6 Since your trial surgery have you visited a hospital for appointments to see any other staff because of your knee?

No □ Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th>Other hospital staff seen in last 2-3 months</th>
<th>How many times?</th>
<th>Who paid for your treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiotherapist</td>
<td></td>
<td>NHS □ myself/relative □ insurance □ employer □</td>
</tr>
<tr>
<td>Occupational therapist</td>
<td></td>
<td>NHS □ myself/relative □ insurance □ employer □</td>
</tr>
<tr>
<td>Other staff <em>(please specify below)</em></td>
<td></td>
<td>NHS □ myself/relative □ insurance □ employer □</td>
</tr>
</tbody>
</table>

Q7 When you visited the hospital since your trial surgery did someone come with you, for example your spouse/partner, a relative or friend?

Yes □ No □

Q8 When you last visited this hospital how many miles did you travel in total? (also write where you travelled from and to)

_____ miles for one round trip from __________________________ to _________________________

VISITS TO OR FROM GENERAL PRACTICE OR OTHER NHS TREATMENT OUTSIDE THE HOSPITAL

Q9 Since your trial surgery have you visited your GP or other staff in the GP surgery or the community (e.g. physiotherapy in another community facility) because of your knee?

No □ (If no, go to Q11) Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th>Other staff (please specify below)</th>
</tr>
</thead>
</table>

Please turn over the page
Q10 When you visited the General Practice since your trial surgery did someone go with you, for example your spouse/partner, a relative or friend?

Yes □ No □

Q11 Since your trial surgery have you been visited at home by your GP, or any other NHS health professional because of your knee?

No □ Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th></th>
<th>How many times?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
</tr>
<tr>
<td>Practice Nurse</td>
<td></td>
</tr>
<tr>
<td>District Nurse</td>
<td></td>
</tr>
<tr>
<td>Community Physiotherapist</td>
<td></td>
</tr>
<tr>
<td>Other staff (please specify below)</td>
<td></td>
</tr>
</tbody>
</table>

Q12 Since your trial surgery have you had a telephone consultation with your GP, or any other NHS health professional because of your knee?

No □ Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th></th>
<th>How many times?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
</tr>
<tr>
<td>Practice Nurse</td>
<td></td>
</tr>
<tr>
<td>Other staff (please specify below)</td>
<td></td>
</tr>
</tbody>
</table>

OTHER PROFESSIONALS SEEN PRIVATELY
Q13 Since your trial surgery have you seen any professionals privately because your knee?

No □ Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th></th>
<th>How many times?</th>
<th>Total cost?</th>
<th>Who paid for your treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiotherapist</td>
<td></td>
<td>£</td>
<td>myself/relative □ insurance □ employer □</td>
</tr>
<tr>
<td>Complementary therapist (e.g. acupuncturist, reflexologist)</td>
<td>£</td>
<td></td>
<td>myself/relative □ insurance □ employer □</td>
</tr>
<tr>
<td>Other professional (specify below) e.g. osteopath</td>
<td>£</td>
<td></td>
<td>myself/relative □ insurance □ employer □</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>£</td>
<td></td>
</tr>
</tbody>
</table>
MEDICATION
Q14 Since your trial surgery have you taken any medication for your knee?

No □ Yes □ If yes, please complete below. For the last column, if you paid for prescriptions yourself please estimate the total cost for the last 2-3 months since your trial surgery.

<table>
<thead>
<tr>
<th>Name of medication (can include tablets, cream, mixture)</th>
<th>Was this prescribed by the doctor (Doc) or bought over the counter? (OTC) (delete one)</th>
<th>Strength e.g. 300mg</th>
<th>Dose How many tablets did you take at a time? (e.g. 2 tablets)</th>
<th>Times per day e.g. twice per day</th>
<th>Duration How long have you used this in the last year? (e.g. all year; 1 month; 2 weeks)</th>
<th>Cost to you How much did you spend on each medication? (e.g. £30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc / OTC</td>
<td>£</td>
<td>Doc / OTC</td>
<td>£</td>
<td>Doc / OTC</td>
<td>£</td>
<td>Doc / OTC</td>
</tr>
</tbody>
</table>

ADDITIONAL COSTS BECAUSE OF YOUR KNEE
Q15 Since your trial surgery have you incurred any other costs because of your knee? e.g. paid for help with work/jobs you couldn’t do because of your knee or bought any aids and appliances to help with your knee (e.g. recliner chair)

No □ Yes □

If yes, what were they for and how much did you spend? In the table below please write the purpose of these costs and an estimate of the amount of money you spent since your trial surgery.

<table>
<thead>
<tr>
<th>Purpose (e.g. had to employ a gardener because of my knee / Item (e.g. bought a chair)</th>
<th>Amount spent (e.g. £500)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£</td>
</tr>
<tr>
<td></td>
<td>£</td>
</tr>
<tr>
<td></td>
<td>£</td>
</tr>
</tbody>
</table>

EMPLOYMENT
Q16 What is your current work situation?

1 Employed / self-employed full-time □ 2 Employed / self-employed part-time □ 3 Homemaker □ 4 Student □ 5 Unemployed □ 6 Retired □ 7 Voluntary work □ 8 Unable to work/claiming disability benefit because of knee □ 9 Other (please specify): ____________________________________________

Please turn over the page
Q17 If you are in paid work/self-employed what is your job? (please give title and description)
________________________________________________________________________
________________________________________________________________________

Q18 How many hours per week are you currently in paid employment or are self-employed?
______ hours per week

Q19 Since your trial surgery how many days and months have you had to take off work because of your knee?
(your knee diary may help you)
______ days and _____ months

Q20 If your spouse/partner, a relative or friend accompanies you to hospital or General Practice visits, or helps you in other ways, is this person/are these people in paid employment?
Yes □ No □ (continue to question 23)

Q21 If yes, how many hours per week do they work?
______ hours per week

Q22 Since your trial surgery how many days has your spouse/partner, a relative or friend had to take off work because of your knee?
______ days

Q23 Has your work situation now changed because of your knee?
No □ Yes □ (If yes, please complete below)

<table>
<thead>
<tr>
<th>Changes in my work because of my knee</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Working fewer hours per week because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>2 Doing lighter, less physically demanding work because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>3 A change in occupation because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>4 Less job security now because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>5 Reduced income because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>7 Have been made redundant because of my knee</td>
<td>No □ Yes □</td>
</tr>
<tr>
<td>8 Other (please state)</td>
<td>No □ Yes □</td>
</tr>
</tbody>
</table>

Thank you for your help.
Please check you have answered all the questions before returning this pack.
SERIOUS ADVERSE EVENT FORM

For the purpose of this study a “serious” adverse event is one which occurs within one year of the end of treatment for the affected knee and is either:

Deep vein thrombosis, a fall causing injury, infection to the knee joint
Or
Causes death, hospitalisation (or extension to hospital stay), persistent or significant disability, permanent impairment of function, or treatment to prevent permanent impairment of function.
Or
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

Please report immediately any serious events by telephoning the Trial Office on +44 (0)1691 404142 and giving the following information:

Patients Full Name: ....................................................................................................................
Date of Birth: ................................................ Hospital Number: ........................................
Responsible Doctor: ...................................................................................................................
ACTIVE Trial Number: ...........................................
Date event started: ...........................................
Outcome (e.g. fatal, recovered, continuing) ...........................................................................

Details of adverse events (please attach copies of relevant reports)
...................................................................................................................................................
...................................................................................................................................................
...................................................................................................................................................

Did the event require hospitalisation? Yes ☐ No ☐
Do you believe this event is related to the treatment? Yes ☐ No ☐
If yes please give reasons why you consider the event to be treatment-related:
...................................................................................................................................................
...................................................................................................................................................
...................................................................................................................................................

Name of person making report (please print) .........................................................
Telephone No:.............................. Today’s date:..............................

When you have made the telephone call, please FAX this form (with copies of any relevant reports) to:

Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire, SY10 7AG. Fax: 01691 404170
Stage 1: Initial invitation
During your appointment at the outpatient clinic the Orthopaedic Consultant decided you might be suitable for the trial and described the treatment options to you. You were given this Patient Information Leaflet to take home.

Stage 2: Informed consent
Within 3 months prior to your surgery date you attend an appointment at the hospital with the study coordinator who describes the trial to you and answers any queries you have. You also have an opportunity to speak to the Orthopaedic Consultant again if you wish. If you decide to participate in the trial you will give written informed consent. This stage may coincide with Stage 3.

Stage 3: Pre-randomisation assessment
You attend the clinic prior to your operation where a physiotherapist will assess you to find out how you are affected by your knee condition. You will also be asked to spend about 20 minutes filling in some questionnaires about your knee condition and will receive a diary to take home. This assessment may coincide with your routine pre-operative assessment.

Stage 4: Treatment allocation
The study coordinator will let you know which treatment you were randomly allocated to receive.

Stage 5: Your operation
You have your knee operation. If you are having the cell grafting option you have a second operation at least 3-4 weeks later. You receive a rehabilitation advice leaflet and will see a physiotherapist locally for up to six weeks.

Stage 6: Follow-up over ten years
After your operation you attend the usual follow-up clinics and see the surgeon as appropriate. A physiotherapist will assess your progress and will ask you to fill in the study questionnaires. These clinic visits will be at 2-3 months, 6 months and 12 months after your operation.

After Stage 6 you will be contacted annually to complete the questionnaires for the trial and at 3, 5 and 10 years after your operation you will attend the hospital to be assessed by the physiotherapist.

APPENDIX 10A

Autologous Chondrocyte Transplantation / Implantation Versus Existing treatments

www.active-trial.org.uk

Patient Information Leaflet
For individuals invited to take part in the trial

Version 3.1 February 2008
INTRODUCTION
You have been invited to take part in a research study. It is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask us. Take as much time as you need to decide whether or not you wish to take part.

PURPOSE OF THE STUDY
Defects in the cartilage covering the bones of the knee do not heal by themselves. A technique to treat cartilage defects called autologous chondrocyte implantation (also known as ACI or cartilage cell grafting) was developed in Sweden and has been used on many patients in the UK, and US. This treatment appears to have been successful in treating many patients but has not yet been tried and tested in a formal trial. A newer version of ACI has been developed, known as matrix-assisted ACI (MACI) which is technically easier for the surgeon to perform and slightly less invasive than the traditional technique. Your surgeon will discuss with you which type of ACI therapy he plans to use.

WHY HAVE I BEEN INVITED?
You have been invited to take part in the trial because you are still getting symptoms from the defect in your knee cartilage, even though you have had surgical treatment for it in the past. We aim to recruit at least 420 patients in the UK and 60 patients in Norway.

DO I HAVE TO TAKE PART?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information leaflet to keep and will be asked to sign a consent form. You would still be free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or not to take part, will in no way affect the standard of care you receive.

Thank you for reading this.

You will be given a copy of this INFORMATION LEAFLET and if you agree to take part, a copy of the signed consent form to keep. Further information about the ACTIVE trial is available on the website: www.active-trial.org.uk

CONTACT FOR FURTHER INFORMATION
Local Coordinator
..................................................................................................
or Local Principal Investigator
..................................................................................................
or Chief Investigator
Professor James Richardson
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Tel: Janet Morris (sec) 01691 404386

or Trial Manager
Dr Heather Smith
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Tel: 01691 404142
RISKS AND BENEFIT
If you are allocated to the cartilage cell grafting group this involves a 2-stage procedure, so you will have two operations under general anaesthetic. In addition to the normal risks of knee surgery there is a small risk that you may experience an allergic reaction to a substance used in the cell transplantation. However, this reaction is very rare. We hope that whichever treatment you have will help you. However, this cannot be guaranteed. The information we get from this study may help us to recommend the best course of action for patients like you in the future.

As with other research trials of this kind, should taking part in this research project harm you, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

CONFIDENTIALITY
We will notify your GP that you are participating in the trial. All information that is collected about you during the course of the research will be entered into the ACTIVE Trial database by study staff and kept strictly confidential. We will need to access your hospital records so that we can collect information on any subsequent surgery or treatment you have on the same knee. If you have the cell grafting treatment your cells will only be used for your treatment, they will not be stored and used for any other purpose.

WHAT HAPPENS TO THE RESULTS?
The results will be regularly reviewed by an independent Data Monitoring and Ethics Committee. The Committee can stop the study if it is clear that any group of patients is being disadvantaged. At the end of the study the results will be published. You will not be identified in any way.

WHO FUNDS THE STUDY?
The Medical Research Council is funding the research costs of the study. None of the doctors looking after you will be paid for including you in the study.

The North Staffordshire Multicentre Research Ethics Committee has approved this study.

WHAT HAPPENS IF I DO DECIDE TO TAKE PART?
Sometimes if we do not know what is the best method of treatment for patients, we need to make comparisons. If you do decide to take part in the trial you will be put into one of two groups. One group will have the cartilage cell grafting treatment and the other group will receive the most appropriate alternative treatment. The groups will be allocated by computer, i.e. by random chance so there will be a 50:50 chance as to which group you will be in. You will have a full assessment of your knee and be asked to complete questionnaires about your knee function and how it affects your quality of life.

If you are allocated to the cartilage cell grafting group, you will have a 2-stage operation. Both operations will be carried out under general anaesthetic. The first operation is keyhole surgery during which a small sample of healthy cartilage is taken from the knee to a laboratory for the cells to be grown. The cells are grown in a sterile medium with growth factors or in a medium containing your own blood. After 3-5 weeks, there should be sufficient cells to transplant back into the cartilage defect in your knee. If your own blood is used in the medium then we will take 100ml of your blood (about half a cup full) before the first operation.

At the second operation the knee is opened and any loose cartilage is removed from the defect and a patch is stitched over it. The patch will either be periosteum (the membrane which covers the surface of your bones) or it will be a collagen membrane. If the patch is periosteum, this is removed from your shin through a small additional incision just below your knee. Sometimes the periosteum thickens and a further operation may be required later to reduce the thickening once the cells have regenerated. A newer procedure, in use for 9 years, is a patch made from pig collagen (a fibrous protein found in skin and cartilage). One advantage of this is that an additional incision is not required so you will not have the possible discomfort in your shin. However there has not yet been a long-term trial of this type of patch in comparison with periosteum.

The cells grown in the laboratory are then injected into the defect behind the patch and the knee is closed with sutures. If you are having MACI the cells are grown on collagen membrane in the laboratory, and then the membrane is secured over the defect in your knee using a tissue fibrin sealant without using stitches unless they are necessary.

If you are allocated to the alternative treatment group your surgeon will discuss the treatment options with you before selecting one. These
treatments are debridement, microfracture/drilling, or mosaicplasty. They are all carried out under general anaesthetic and have been in use for 5-10 years. A newer treatment called AMIC (Autologous Matrix Induced Chondrogenesis) is also an alternative option in the trial. AMIC is similar to a standard microfracture except that it also involves attaching a membrane (made from pig collagen) over the defect to keep the blood in the damaged area of cartilage. Your surgeon will explain the alternative treatments in full and together you can decide which one is best for you.

BLOOD TESTING
All patients who have cell treatments in the UK must have a blood test to show that they are HIV, hepatitis B, hepatitis C, and syphilis negative. You may also be tested for human lymphotrophic virus (HTLV I & II). For these tests, 8ml (about 2 teaspoons) of your blood will be needed and this is taken either on the day you give consent to enter the trial or at the first stage of ACI. If you have a positive result you may not be able to have cell therapy and your surgeon will discuss this with you. Since 1994 the Association of British Insurers has stated that a negative HIV test does not affect an insurance application. However, if you test positive for HIV your ability to take out life insurance or a mortgage will be affected. Counselling will be available to you before and after the test if you wish.

WHEN WILL I KNOW WHAT GROUP I WILL BE IN?
When you have decided to participate and have signed a consent form you will be registered for the trial. You may be randomised at this stage and will be informed of which treatment group you have been allocated to. If your treatment is expected to be delayed for more than 6 months, you will be randomised and allocated to a group nearer the time of your operation, and you will be informed as soon as this happens.

HOW LONG WILL I BE IN HOSPITAL?
Debridement or drilling and cartilage grafting Stage-1 are usually undertaken as a day-case procedure. Microfracture and AMIC generally require a 1 day stay in hospital while mosaicplasty or cartilage grafting Stage-2 generally require a 2 day stay in hospital. It may also be necessary for you to stay in hospital the night before any of these procedures. Following microfracture, AMIC and Stage-2 ACI a special machine will be fitted to your leg to keep the knee moving while you are in bed but you will not need to stay in bed all the time while in hospital.

WHAT HAPPENS AFTER SURGERY?
Whichever group you are in, you will have the standard physiotherapy and rehabilitation programme that is best for the treatment you received. After you are discharged you will not be required to attend any further physiotherapy but you will be expected to do your best to follow your recommended programme. Generally, crutches are needed initially, and this may vary from 1 week to 2 months depending on your treatment. Rehabilitation following the cartilage grafting treatment is likely to be slower than the other treatments because the cells need time to generate repair tissue. You should avoid driving for 7 weeks but how long you are off work will depend on the nature of your employment. If your work is very strenuous, you may be off for several months. If you wish to resume high contact sports such as rugby, the recommended rehabilitation period is approximately 12 months but the surgeon will advise you on this before you decide whether to take part in the trial. All patients, whichever treatment they receive, will be given a follow-up appointment 2 or 3 months after surgery and again at 6 months and at 1 year after surgery. This will give your surgeon a chance to see how you are progressing. On each occasion you will be asked to complete some questionnaires and your knee function will be measured by a research assessor who will not know which treatment you had. It is important that you do not tell the assessor what treatment you had, and that you wear a stocking (which will be provided) to cover both your knees so the assessor cannot be influenced by the knowledge of which treatment you have had.

Because we want to compare the long-term outcome of the treatments we will ask you to return to the clinic 3 years, 5 years and 10 years later. This will also alert the surgeon to any problems you may have, whichever treatment you received. We also ask that you agree to let us contact you by post, phone or e-mail on one occasion each year for 10 years so we can check on your progress. Although this sounds like a long time, your cooperation is vital to the success of the trial so it is very important that we can remain in contact with you. If you have difficulty getting to the hospital for a follow-up visit at the proper time, the assessor may be able to arrange to visit you at home.

You will not be asked to take any special medication except that which is normally necessary for your surgery. After you are discharged you will be able to take any other medication that is prescribed or recommended for you. You will not be prevented from having any further treatment on your knee if your condition warrants it, whichever group you are in.

A schedule of your journey through the trial is presented on the back page of this leaflet.
PATIENT CONSENT FORM

Study Number: ISRCTN 48911177  Centre Name: .................................................................

Principal Investigator: .................................................................

Please initial the boxes

1. I confirm that I have read and understand the information sheet dated February 2008 (version 3.1) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the trial team where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

5. I agree to take part in the above study.

Name of Patient _______________________________ Date _______________________________ Signature _______________________________

Name of Person taking consent _______________________________ Date _______________________________ Signature _______________________________

Name & address of Patient’s GP:
....................................................................................................................................................

Postcode: .............................................  Tel. No: .................................................................

Three copies of this consent form are needed:
Top (white) copy to be kept in the patient notes
Yellow copy to be kept by the patient
Pink copy to be forwarded to the study coordinator
Dear Dr

Your above named patient has agreed to take part in ACTIVE, a randomised trial of different surgical procedures for a chondral or osteochondral defect in the knee in which we, and many other centres in the UK, are collaborating.

The trial aims to compare the long-term benefits and costs of autologous chondrocyte implantation (ACI or cartilage cell grafting) with the “best alternative” from a range of other surgical treatments such as mosaicplasty, microfracture and debridement.

The trial is organised by the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry together with the University of Birmingham Clinical Trials Unit and is funded by the Medical Research Council and supported by the Department of Health.

Patients are eligible for the trial if they have had a previous surgical intervention for the defect more than 6 months ago that has not relieved symptoms. All of the treatment alternatives have been explained to your patient who was randomly allocated the following treatment:

□ Cartilage cell grafting with periosteum   □ Cartilage cell grafting with membrane
□ Debridement    □ Mosaicplasty   □ Microfracture   □ Drilling    □ Abrasion    □ AMIC

Cartilage cell grafting requires two operations approximately 3-5 weeks apart. In the first stage (day case), a small sample of cartilage is removed from the knee, cells are removed and amplified in the laboratory. At the second stage (2 day in patient stay) the cells are transplanted back into the knee and retained in place either by a patch of periosteum removed from the shin, or by a porcine collagen patch. Mosaicplasty, the transplant of a chondral plug from a non-load bearing area of the knee into the defect also necessitates a 2-day in patient stay. Microfracture and AMIC usually requires a 1-day in-patient stay while debridement and drilling are usually carried out as day cases.

PTO
Following surgery your patient will follow a rehabilitation programme appropriate for the allocated procedure. There are no requirements or restrictions on medication nor will the patient be prevented from having any further treatment for the same problem if that becomes necessary. Follow up will comprise assessment of knee function by an observer who has no knowledge of the treatment allocation, and by self-assessment questionnaires completed by the patient. The follow-up will take place at intervals in the outpatient clinic, and by post, for 10 years. No additional invasive tests or radiology are required.

If you require any further information about the trial please contact me or the study co-ordinator

Yours sincerely,

------------------------------------------------- 
Consultant Orthopaedic Surgeon
Tel:
## Treatment Record

<table>
<thead>
<tr>
<th>Active Trial Number</th>
<th>Patient's Initials:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Number:</td>
<td>Date of Birth:</td>
</tr>
<tr>
<td>NHS Number:</td>
<td>Sex: M / F</td>
</tr>
</tbody>
</table>

| Surgeon: |

---

### Diagram:
- **Right Leg:**
  - Lateral view
  - Anterior view
  - Roti Edges (in degrees)
- **Left Leg:**
  - Lateral view
  - Anterior view
  - Roti Edges (in degrees)

- **Articular cartilage degeneration:**
  - Grade I
  - Grade II
  - Grade III
  - Grade IV (Bone)
**Treatment Record**

**PATIENTS’S MEDICAL DETAILS**

Where is the defect? (please tick)

<table>
<thead>
<tr>
<th></th>
<th>Medial femoral</th>
<th>Lateral femoral</th>
<th>Trochlear</th>
<th>Patella</th>
</tr>
</thead>
</table>

Which knee: (please tick)

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
</table>

Duration of symptoms: months/years

**Tick the box if you agree with the following statements:**

- The patient has generalised OA:
- The patient has untreated malalignment of the patella or an unstable knee:
- The patient had a concurrent total meniscectomy or osteotomy:
- The patient has kissing lesions:

**DETAILS OF ACTUAL TREATMENT**

<table>
<thead>
<tr>
<th>Please tick</th>
<th>Debridement</th>
<th>Abrasion</th>
<th>Drilling</th>
<th>Micro#</th>
<th>AMIC</th>
<th>Mosaicplasty</th>
<th>ACI</th>
<th>MACI</th>
<th>Chondron</th>
</tr>
</thead>
</table>

Date of treatment:

<table>
<thead>
<tr>
<th>Treatment:</th>
<th>/</th>
<th>/</th>
</tr>
</thead>
</table>

If ACI/MACI, date of stage II

| / | / |

Actual defect* size before debridement:

| ( x ) cm (or) cm² |

Depth of defect: (bone depth only)

| mm |

Defect size after debridement:

| ( x ) cm (or) cm² |

*NB if more than one defect give size of largest defect

**FOR ACI**

<table>
<thead>
<tr>
<th>Please tick</th>
<th>Medial Ridge</th>
<th>Lateral Ridge</th>
<th>Intercondylar Notch</th>
</tr>
</thead>
</table>

If periosteum used which site:

<table>
<thead>
<tr>
<th>Tibial Periosteum</th>
<th>Femoral Periosteum</th>
</tr>
</thead>
</table>

If membrane used which type:

<table>
<thead>
<tr>
<th>Chondro-Gide</th>
<th>Other (specify):</th>
</tr>
</thead>
</table>

Was fibrin sealant used?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

Number of cells used:

| million |

Please score 1 to 10; 10 being the best

<table>
<thead>
<tr>
<th>Water tightness</th>
<th>Suture security</th>
</tr>
</thead>
</table>

Self-score for:

**FOR MACI/Chondron**

<table>
<thead>
<tr>
<th>Please tick</th>
<th>MACI (Genzyme)</th>
<th>Chondron</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Type of MACI</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Medial Ridge</th>
<th>Lateral Ridge</th>
<th>Intercondylar Notch</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Biopsy site</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Number of cells used:</th>
</tr>
</thead>
</table>

Please score 1 to 10; 10 being the best

<table>
<thead>
<tr>
<th>Self-score for stability:</th>
</tr>
</thead>
</table>

**FOR MOSAICPLASTY**

**Instruments used for mosaicplasty:**

**Size of donor site**

| ( x ) cm² |

Number of grafts

**Please score 1 to 10; 10 being the best**

<table>
<thead>
<tr>
<th>Fill</th>
<th>Surface smoothness</th>
</tr>
</thead>
</table>

Self-score for:

**OSTEOCHONDRAL DEFECTS REQUIRING BONE GRAFTING**

(for defects with more than 3mm of bone loss and/or Subchondral bone sclerosis)

Depth of bone loss prior to grafting

| mm |

Depth of bone loss after grafting

| mm |

Please tick type of graft and whether sandwich technique was used

<table>
<thead>
<tr>
<th>Autologous</th>
<th>Allogenic</th>
<th>Substitute (specify make)</th>
<th>Sandwich method</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Type of bone graft</th>
</tr>
</thead>
</table>

**For All Procedures**

If patient did not receive their allocated treatment please give reasons or any other comments:

**Please forward one copy of this form to your local trial co-ordinator and keep the original form with the patient’s notes.**

**Copy made for Co-ordinator:**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

**Name of Surgeon**

<table>
<thead>
<tr>
<th>Signed:</th>
<th>Date:</th>
</tr>
</thead>
</table>

**For Study Co-ordinator:**

Please post a copy of this form to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry, SY10 7AG. Please ensure that the original form is securely filed.