AUTOLOGOUS **S**TEM CELLS, **C**HONDROCYTES, **O**R THE **T**WO?

ASCOT

ASCOT is a Clinical Trial of an Investigational Medicinal Product with authorisation from the MHRA, ethical approval from the West Midlands Local Research Ethics Committee and funding from the Medical Research Council, Arthritis Research UK and others.

Sponsor	Robert Jones & Agnes Hunt Orthopaedic NHS Trust
Chief Investigator	Mr Peter Gallacher
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ASCOT is a Phase II **prospective randomised trial** designed to determine if modification of standard autologous chondrocyte implantation (ACI) by the use of other cell types will improve its outcome. The trial will compare autologous chondrocytes with either autologous bone marrow-derived stromal cells (BMSCs) or a combination of the two, when implanted beneath either a periosteal or a collagen membrane for the treatment of articular cartilage defects in the knee.

Outcomes:

The ***primary outcome measure*** will be the functional knee score (patient-reported Lysholm score) at 15 months post-treatment, compared to baseline pre-treatment values.

Secondary outcomes will be (i) the incidence of adverse events, (ii) structural quality of the repair tissue, (iii) other health-related quality of life assessments and (iv) a cost-utility analysis.

Randomisation, blinding and statistical analysis:

The **target recruitment is 114 patients** over 4 years. This is a single-centre study to be carried out in the Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust, Oswestry, Shropshire.

ACI patients will be randomised to 3 arms, each with 37 participants:

- Standard autologous ACI procedure using autologous chondrocytes for implantation or
- Modified ACI using autologous BMSCs for implantation or
- Modified ACI using both autologous chondrocytes and BMSCs for implantation.

Treatment will be allocated by stratified randomisation. Stratification will be based on known predictors of functional outcome (pre-operative knee score, defect location, gender and age).

The sample size is sufficient to test the study hypotheses with 80% power at the p=0.05 level, based on detecting the minimal clinically important difference (MCID) in Lysholm knee scores.

Participants will be blinded to the treatment they have been allocated. All scoring of outcome measures performed by the research team will be done by members of the team who are blinded to the treatment allocation.

Inclusion Criteria:

I. A symptomatic defect of the knee that exposes, or extends to or into, the subchondral bone (ICRS classification 3 or 4).

II. The patient is aged between 18 and 80 years at the time of surgery.

III. Treatment with ACI must be appropriate for the patient.

IV. Surgical treatment (eg debridement, abrasion, drilling, microfracture) may have been performed on the same defect at least 6 months previously and failed to relieve symptoms.

V. The patient is able to provide written informed consent to participate in the trial.

Exclusion Criteria:

I. Not adequately understanding verbal explanations or written information given in English, or having special communication needs.

II. Likely to show contraindications to autologous cell therapy: Inflammatory arthritis, previous or current malignant tumour, therapy with steroids or methotrexate, opioid or anti-coagulant medication use that cannot be stopped prior to surgery, bleeding tendency or known anaphylaxis to any product used in chondrocyte preparation.

III. Low probability of compliance with physiotherapy or follow-up, including a major life-threatening condition, as assessed by the research team.

IV. A defect of greater than 20cm^2 in total area.

V. The patient is shown to be positive for serology tests required by the cell provider. This includes HIV, hepatitis B and C, syphilis, and human T cell lymphotrophic virus (HTLV) I & II.

VI. Pregnancy or lactation.

Risks:

As with all medical and surgical treatments, there is some inherent risk, as determined in the bespoke Clinical Trial Risk Assessment that has been performed as required by the MHRA. Benefits to patients in all arms of the trial are expected to be at least as good as those of standard ACI, performed previously in our centre and other centres since 1996.

Post-operative rehabilitation and clinical follow-up:

Appropriate rehabilitation is essential whichever treatment is allocated. For all three arms of this trial, the OsCell recommended protocol for rehabilitation is identical and will be made available to the patient, GP and physiotherapist.

All patients will attend a clinical review at 2 months, 12 months and 15 months following surgery, and will be asked to complete knee scores and quality of life questionnaires at each visit. Participants will also be asked to attend for an MRI and CT scan and an arthroscopy with biopsy of repair tissue at around 13 months following surgery.

Funding

NHS Treatment Costs associated with research studies, including Excess Treatment Costs, are the responsibility of the NHS and should be funded through normal commissioning arrangements.

Participant flow chart

Visit 1: Patient requests information in response to press
- PIL and letter sent to patient by post
- Patient referred to local orthopaedic surgeon by GP
- Patient referred to RJAH if considered suitable for ACI by local orthopaedic surgeon

Visit 2: Follow-up telephone call by researcher approximately 1 week later
- Eligibility criteria checked

Visit 3: Diagnostic MRI scan if not done previously

Visit 4: Consent and Baseline (outpatient clinic)
- Eligibility criteria checked (including MRI results) and documented in notes
- Serology blood samples taken if not taken previously
- Informed consent discussion takes place with research nurse
- Consent form is signed by patient and investigator
- Baseline questionnaires completed by participant

Randomisation
- Stage 1 and 2 surgery booked
- Research MRI and CT booked

Visit 5: Preoperative assessment clinic:
- Research MRI and CT scan (or at day of admission for stage 1)

Visit 6: Stage 1 surgery – Biopsy harvest
- Baseline questionnaires repeated by participant
- Pregnancy test
- Blood collection for preparation of autologous serum
- Synovial fluid and blood collection for Biomarkers
- Surgical data collection
- Adverse events

Time from imaging to Stage 1:

Max. 3 months.

Visit 7: Stage 2 surgery – Cell implantation
- Synovial fluid and blood collection for Biomarkers
- Surgical data collection
- Adverse events

Visit 8: Daily checks during inpatient stay
- Adverse events

Visit 9: Day of discharge
- Length of stay

Visit 10: Telephone call 1 week after discharge (+/- 2 days)
- Adverse events

Visit 11: 2 month clinical review (6 – 10 weeks post-op)
- Adverse events
- Knee scores and Quality of life questionnaires
- Rehabilitation review

Visit 12: 12 month clinical review (+/- 4 weeks), and pre-operative assessment for arthroscopy and biopsy
- Knee scores and Quality of life questionnaires
- Rehabilitation review
- Serious adverse event (SAE) collection

Visit 13: Imaging, arthroscopy & knee biopsy at 13 months (+/- 4 weeks)

Synovial fluid and blood collection for biomarkers
- MRI scan
- CT scan
- Arthroscopy and Repair tissue biopsy

Visit 14: 15 month clinical review (+/- 4 weeks)
- Discussion of MRI scan, arthroscopy & biopsy results
- SAE collection
- Knee scores and Quality of life questionnaires
- Rehabilitation review