An Investigation into Meniscal Allograft Transplantation for the Treatment of the Symptomatic Meniscal Deficient Knee

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This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been compiled solely by me and has not been submitted in any previous application for any degree.

The work presented (including data generated and data analysis) was carried out by me except in the cases outlined below:

Chapter 3: The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Nicola MacKay.

Chapter 4: The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Ben Parkinson.

Chapter 5: The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Imran Ahmed.

Chapter 6: The patient data was prospectively collected by the knee team as part of a service evaluation.

Chapter 7: The randomisation sequence was created by Nick Parsons (statistician). The surgical intervention protocol was written with the help of Tim Spalding (surgeon). The personalised knee therapy protocol was written with the help of David Wright (physiotherapist). The MRI sequence protocol was created by Charles Hutchinson (radiologist).

Chapter 8: Research associates collected questionnaires from participants.
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<thead>
<tr>
<th>Abbreviations</th>
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<tr>
<td>3D</td>
<td>Three dimensional</td>
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<tr>
<td>%</td>
<td>Per cent</td>
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<td>AAM</td>
<td>Active appearance model</td>
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<tr>
<td>ACI</td>
<td>Autologous Chondrocyte Implantation</td>
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<td>ACL</td>
<td>Anterior cruciate ligament</td>
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<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>Cochrane Central Register of Controlled Trials</td>
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<td>CH</td>
<td>Charles Hutchinson</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CSRL</td>
<td>Clinical Sciences Research Laboratories</td>
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<tr>
<td>dGEMRIC</td>
<td>Delayed gadolinium enhanced magnetic resonance imaging of cartilage</td>
</tr>
<tr>
<td>GAG</td>
<td>Glycosaminoglycans</td>
</tr>
<tr>
<td>HSS</td>
<td>Hospital for Special Surgery</td>
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<tr>
<td>ICRS</td>
<td>International Cartilage Repair Society</td>
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<td>IH</td>
<td>Ivor Hughes</td>
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<td>International Knee Documentation Committee</td>
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<td>International Meniscal Reconstruction Experts Forum</td>
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<tr>
<td>KAM</td>
<td>Knee adduction moment</td>
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<td>KL</td>
<td>Kellgren and Lawrence</td>
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<td>KOOS</td>
<td>Knee injury and Osteoarthritis Outcome Score</td>
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<tr>
<td>LCL</td>
<td>Lateral collateral ligament</td>
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<td>MAT</td>
<td>Meniscal allograft transplantation</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MC</td>
<td>Matthew Costa</td>
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<tr>
<td>MCID</td>
<td>Minimum Clinically Important Difference</td>
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<td>MM</td>
<td>Millimetres</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MRI</td>
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</tr>
<tr>
<td>MSEC</td>
<td>Millisecond</td>
</tr>
<tr>
<td>N/A</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>National Institute for Health and Care Excellence</td>
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<td>National Institute for Health</td>
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<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<td>NS</td>
<td>Nicholas Smith</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<td>OAI</td>
<td>Osteoarthritis Initiative</td>
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<td>PCL</td>
<td>Posterior cruciate ligament</td>
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<td>PG</td>
<td>Preference group</td>
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<td>Participant Information Sheet</td>
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<td>Personalised knee therapy</td>
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<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
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<td>PROM</td>
<td>Patient reported outcome measure</td>
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<td>PT</td>
<td>Peter Thompson</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>SF-36</td>
<td>Short Form (36) Health Survey</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>TL</td>
<td>Transverse ligament</td>
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<td>Trial Management Group</td>
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<td>TS</td>
<td>Tim Spalding</td>
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<td>University Hospitals Coventry and Warwickshire</td>
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<td>Versus</td>
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<td>WOMAC</td>
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Meniscectomy is a common treatment for a young patient with a traumatic meniscal tear, despite the known negative consequences. Meniscal allograft transplantation has been performed for over thirty years in young symptomatic patients following a meniscectomy but it has never been rigorously evaluated for effectiveness. Therefore the aim of this thesis was to perform the development and pilot work to inform a future multi-centre pragmatic randomised controlled trial comparing meniscal allograft transplantation to physiotherapy.

Systematic reviews in this thesis showed that in case series, meniscal allograft transplantation resulted in improved patient reported outcome measures in the short and medium term, although there were no comparator groups. There was no strong evidence for chondroprotection with either meniscal allograft transplantation or physiotherapy in this patient population.

In the systematic review it was also identified that full thickness cartilage lesions were a contraindication to meniscal allograft transplantation for most surgeons. A Cox proportional hazards model was used on a case series of meniscal allograft transplantations performed locally, which showed that a full thickness cartilage lesion was a strong predictor of failure. It was therefore determined that these patients should be excluded from the pilot trial.

A comprehensive cohort study incorporating a pilot randomised controlled trial was performed, with 36 participants being recruited over one year. The trial processes worked successfully and the pilot randomised trial recruitment rate was 55%. There were no losses to follow up in the randomised arm of the trial. Patient reported outcome measures showed a trend towards a bigger improvement in the meniscal allograft transplantation group, which was statistically significant in the KOOS score when the randomised and preference groups were merged. Sample size calculations for the data in the trial using the KOOS score suggest that between 70 and 114 participants would be needed in a full trial.

The results of this thesis suggest that a full trial is warranted and could be deliverable within the UK, with some small adjustments to the trial design.
I have undertaken the following training as part of my study:

1) Integrated Academic Training, University of Warwick, UK
   a) How to Write an Academic Paper
   b) Sample Size Estimations
   c) Study Design
   d) Epidemiology
   e) Patient Reported Outcome Measures
   f) Statistics: Errors and What Not to Report

2) Chief Investigators’ Course, including Good Clinical Practice, University of Warwick, UK

3) Statistical Issues in Design and Analysis of Research Projects, University of Liverpool, UK

4) The Design and Analysis of Randomised Controlled Trials, University of Bristol, UK

5) Clinical Trials of Complex Interventions and Multi-Components Course, University of Warwick, UK
I have attended the following conferences as part of my training:

International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine Annual Conference, Lyon, France

Arthritis Research UK Fellows’ Meeting, Burleigh Court, UK

British Association for Surgery of the Knee Annual Conference, Telford, UK

Sports Knee Surgery, St George’s Park, UK. Organised by Warwick Orthopaedics

West Midlands Surgical Society Autumn Meeting, Good Hope Hospital, UK

Research Grants Obtained

Arthritis Research UK, Clinical Research Fellowship: £180 500 (grant number 20149).

Research Outputs

As part of this thesis, I have had the following publications in peer reviewed journals:


Smith NA, Parkinson B, Spalding T. Meniscal allograft transplantation and meniscal scaffolds; where are we up to now? Orthopaedics and Trauma Journal 2015;29:31-7.


As part of this thesis, I have had the following book chapters published:


As part of this thesis, I have presented my work at the following conferences:


British Association for Surgery of the Knee, Telford UK, 2015. Meniscal Allograft Transplantation: An Analysis of a Consecutive Series of 114 Transplants Based on Pre-operative Articular Cartilage Grade. (Podium)

British Association for Surgery of the Knee, Telford UK, 2015. Can Meniscal Allograft Transplantation Reduce Osteoarthritis Progression? (Eposter)

West Midlands Surgical Society Autumn Meeting, Good Hope Hospital UK, 2014. A systematic review of meniscal allograft transplantation for the treatment of a symptomatic post-meniscectomy knee. (Poster)

Research, Development and Innovation Summit, University Hospitals Coventry and Warwickshire UK. Meniscal Transplantation and its Effect of Osteoarthritis Risk: A Pilot Randomised Trial. (Poster)

As part of this thesis, others have presented work that I have authored at the following conferences:


1 Introduction, Aims and Objectives

Declarations

None.

Funding body

This research was supported by Arthritis Research UK (grant number 20149).

1.1 Introduction

Menisci are complex fibrocartilage structures located between the two tibiofemoral articulations of each knee. Their main role is to distribute the forces through the knee\(^{83}\). Meniscectomy is a common treatment for a meniscal tear, despite a trend towards meniscal preserving surgery\(^{141}\). This is partly because many tears are not amenable to repair and of those that are, there is a high failure rate\(^{200}\).

Meniscectomy is strongly associated with osteoarthritis (OA) of the knee and young symptomatic patients with a history of meniscectomy are a challenge to treat\(^{213}\). These patients meet the definition of OA on clinical grounds alone and are at a high risk of OA progression\(^{177, 296}\). Joint replacement is an effective pain relieving treatment for severe OA of the knee, but is a poor option in a young person. A treatment that is able to improve symptoms and reduce or delay OA progression would be the ideal solution. The National Institute of Health and Care Excellence
(NICE) have reported in their OA guideline that treatments modifying the joint structure in people with OA are likely to improve symptoms and may reduce OA progression\(^{204}\). They also stated that treatments with the potential to do this should be studied using appropriate outcome measures, including magnetic resonance imaging (MRI) and patient reported outcome measures (PROMs).

There are two treatments currently available on the National Health Service (NHS) that may be used to treat patients with a symptomatic meniscal deficient knee: Meniscal allograft transplantation and physiotherapy. Despite this, there has been no definitive evaluation of whether meniscal allograft transplantation may be a better treatment than physiotherapy for this patient population.

1.2 Thesis Aims and Objectives

The overall aim of this thesis was to provide the development and pilot work to inform a definitive evaluation of meniscal allograft transplantation in treating patients with a symptomatic meniscal deficient knee, compared to physiotherapy.

It is widely accepted that randomised controlled trials (RCT) are the best way to determine the effectiveness of a health care intervention\(^{54}\). Meniscal allograft transplantation and physiotherapy are ‘complex interventions’ because they have several interacting components. In 2008 the Medical Research Council (MRC) updated their widely adopted framework for the development, evaluation and implementation of complex interventions in order to help researchers use appropriate methods\(^{54, 75}\). Figure 1-1 details the MRC key stages in the development and evaluation process of a complex intervention.
Figure 1-1: MRC key stages diagram for the development and evaluation of complex interventions

Whilst best practice is to develop interventions systematically and then test them in a structured way, it is accepted that in practice this process may not happen in a structured progressive way\(^7\). This is the case with meniscal allograft transplantation as the intervention has existed and evolved over many years without a true development, piloting or definitive evaluation process. At University Hospitals Coventry and Warwickshire NHS Trust (UHCW) the knee surgeons have adapted the intervention to suit the latest evidence base and local setting. The same is true for physiotherapy; specific physiotherapy techniques have developed over time and these have been adapted for patients with a symptomatic meniscal deficient knee at UHCW into a programme called ‘personalised knee therapy’. Therefore it would not be possible, or even appropriate, to try and modify these interventions. Therefore, a more pragmatic approach of testing the interventions as they existed in their current form was taken.
Despite the constraints, it was still important to perform some development work. There were two key phases needed before a pilot trial could be considered. Firstly, there was a need to identify the theoretical basis for why an intervention may work in order to determine the plausibility or ‘prior probability’ of the proposed intervention being effective\textsuperscript{75}. It is more likely that an intervention will be effective if its mechanism of action is understood and thought to produce a specific clinical effect\textsuperscript{5}. Secondly, the existing evidence base needed to be identified with the use of systematic reviews\textsuperscript{75}. This was necessary to ensure that there was evidence the intervention had a reasonable chance of working. It was also used to identify any recent development of the intervention to ensure that the interventions in the pilot trial were reasonably representative of interventions in other centres. There are a number of aspects of meniscal allograft transplantation considered controversial, for example selecting suitable patients. If a systematic review demonstrated that an aspect of meniscal allograft transplantation performed at UHCW was not broadly representative of most other studies (and was modifiable), a regression analysis of the current case series data could be performed. This would identify whether the controversial part of the intervention was a predictor of a poorer outcome. If it was found to be the case, the intervention in the pilot study could have been be modified. If no significant effect, or a positive effect was found, the intervention would not need to be modified.

The next stage was the feasibility or piloting phase. Although there is considerable overlap, a feasibility study is used to answer the question of whether a RCT can be successfully achieved. It commonly uses a mixed methods approach and is used to identify important parameters that are needed to design a full RCT. These may include willingness of participants and surgeons to take part and the ability to deliver
the interventions. A pilot is usually a small version of the main study and is designed to test whether the processes of the trial can work together, as well as collecting data on the primary outcome measure. It was considered that a RCT was likely to be deliverable for the following reasons: Both interventions were already being delivered on the NHS without major problems; a number of similar RCTs had been successfully delivered from the department; the number of eligible patients could be approximated from a service evaluation over the last two years; the operating surgeons were fully engaged with randomising and delivering the trial. Due to these reasons, it was determined that a pilot trial was most appropriate, as it could assess the variability and distribution of outcome measures in order to inform a sample size calculation for a full RCT. It was also used to identify specific issues with the processes of the trial, which could be addressed, if required, before undertaking a full RCT.

The MRC framework also recognises that where strong patient preferences may exist, non-standard trial designs may be used, for example comprehensive cohort studies. A comprehensive cohort increases the external validity of a study and may improve the precision of the estimate of the variability of the sample.

Therefore the objectives of this thesis were to:

- Identify the theoretical basis for why meniscal allograft transplantation may result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.
• Systematically review the current evidence base for whether it does result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.

• Identify the theoretical basis for why physiotherapy may result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.

• Systematically review the current evidence base for whether physiotherapy does result in a reduction or delayed progression of OA in patients with a meniscal deficient knee.

• Perform a regression analysis of the current series of meniscal allograft transplantations at UHCW to determine significant predictors of failure.

• Develop and undertake a comprehensive cohort study incorporating a pilot RCT comparing meniscal allograft transplantation to personalised knee therapy in patients with a symptomatic meniscal deficient knee.

• Discuss whether a full RCT would be deliverable, in the light of the results of the findings of this thesis.

Objectives one to five contributed to the development stage and objectives six and seven formed the pilot stage. Objectives one and three were met in chapter two by identifying the scientific plausibility of the two interventions. Objective two was met in chapters three and four by systematically reviewing the current evidence base for outcomes following meniscal allograft transplantation, using in patient reported outcomes and OA progression measures respectively. Objective four was met in chapter five by systematically reviewing the evidence base for whether physiotherapy reduces or delays the progression of OA. Objective five was met in chapter six by performing a regression analysis on the current case series of meniscal
allograft transplantations performed at UHCW. Objective six was met in chapters seven and eight by designing and performing a comprehensive cohort study, incorporating a pilot RCT. Objective seven was met in chapter nine by discussing the implications of the findings in this thesis in the context of whether a full RCT would be deliverable.
2 Scientific Plausibility of the Interventions

Declarations

Aspects of this chapter have been published:


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2.1 Meniscus Anatomy and Microstructure

The menisci are two fibrocartilage structures that sit between the tibiofemoral articulations of the knee. In the axial plane they are crescent-shaped and cross-sectionally they are wedge-shaped. They are attached to the tibia by their insertional ligaments in both the anterior and posterior horns, as well as attachments to the deep medial collateral ligament, anterior intermeniscal ligament (sometimes called
transverse ligament) and two menisco-femoral ligaments (Figure 2-1)\textsuperscript{181}. They are also attached to the joint capsule along their convex peripheral rim.

![Figure 2-1: The meniscal root attachments are shown (numbers 1 and 2 - medial; 3 and 4 - lateral). The anterior intermeniscal ligament (transverse ligament (TL)) and cruciate insertions on the tibia are also shown (source: Messner and Gao\textsuperscript{192}).]

The anterior insertional ligament of the medial meniscus is a flat structure, inserting in the anterior intercondylar fossa, just in front of the anterior cruciate ligament (ACL) insertion\textsuperscript{192}. Posteriorly, the insertional ligament is attached to the posterior intercondylar fossa between the posterior insertion of the lateral meniscus and the insertion of the posterior cruciate ligament (PCL)\textsuperscript{192}. The anterior insertional ligament of the lateral meniscus is also attached to the anterior intercondylar fossa, between the lateral intercondylar tubercle posteriorly and the ACL insertion anteriorly. Its posterior insertional ligament attaches posterior to the lateral intercondylar tubercle and anterior to the posterior insertion of the medial meniscus. The anterior intermeniscal ligament attaches to the anterior horns of both menisci, connecting them.
The blood supply to the knee is mainly from the superior and inferior branches of the medial and lateral genicular arteries. Branches from these arteries form a meniscal capillary plexus within the synovial and capsular tissue of the knee. This plexus (on each side) supplies the meniscal horns and peripheral portion of the meniscus. At birth, the whole meniscus has a blood supply, but this is reduced to the horns and outer twenty-five to thirty-three per cent by around eighteen months. After the age of fifty years, the blood supply is reduced to the outer ten to thirty-three per cent. The blood supply is thought to play a crucial role in the ability of a meniscal tear to heal. The vascular outer third is often referred to as the red-red zone, the variable middle third as the red-white zone and the avascular inner third as the white-white zone. Tears in avascular areas have been shown to heal extremely poorly, compared to the vascular region.

The meniscus also has a similar pattern of nerve supply, with the horns and outer two thirds of the body being richly supplied with nociceptors and mechanoreceptors. The inner third of the body does not have a nerve supply.

Although the functions of the medial and lateral menisci are similar, they do have differences. The medial meniscus is often described as ‘C’ shaped, whereas the lateral meniscus is closer to ‘O’ shaped. The medial meniscus is thinner and larger when compared to its lateral counterpart, which is illustrated in a three dimensional (3D) reconstruction in Figure 2-2. The medial meniscus is less mobile, mainly due to its attachment to the deep medial collateral ligament. Bloecker et al. performed a 3D analysis on magnetic resonance imaging (MRI) scans of normal knees, finding
that the lateral meniscus had a greater surface area. They also found that the lateral meniscus covered fifty-nine per cent of the lateral tibial plateau, compared to fifty per cent for the medial meniscus (Figure 2-2). A further study showed that the lateral meniscus carried seventy per cent of the load through the knee, compared to the medial meniscus carrying fifty per cent\textsuperscript{239}.

![Figure 2-2: A 3D reconstruction from MRI images illustrating the differences in shape and tibial plateau coverage between the lateral meniscus (left) and medial meniscus (right) (source: Bloecker et al.\textsuperscript{41})](image)

The menisci are made up of roughly seventy-five per cent water, twenty per cent type one collagen and five per cent other substances, including proteoglycans, elastin and type two collagen\textsuperscript{188, 286}. The microstructure of the meniscus is highly complex and varies depending on anatomical region. Overall, the collagen fibres form a dense framework, with the majority of fibres running circumferentially, and some radially\textsuperscript{51}. Peterson and Tillmann examined the meniscus under a scanning electron microscope and found three distinct layers: A peripheral fibril network with fibres of no specific direction, a lamellar layer and a central main portion of circumferentially orientated fibres\textsuperscript{218}. Andrews et al. used optical projection tomography on bovine menisci, finding that there was a clear transition from an outer meniscus of highly aligned collagenous fibres in the circumferential direction to a woven, less aligned...
structure in the inner meniscus (Figure 2-3)\textsuperscript{10}. They described the outer portion being close to a ligament in structure, with the inner portion being close to hyaline cartilage in structure. Two types of fascicle organisation were seen within the meniscus: Braided and woven\textsuperscript{10}. Braiding, commonly seen in ropes, results in increasing stiffness with increasing deformation of the fascicles. This is because they compress around each other creating increased friction between them. This would be well suited to the circumferential stress that the meniscus is put under during loading; also known as hoop stress\textsuperscript{48}. A woven structure is commonly used to withstand compressive loads by converting compressive forces into tensile forces, such as a woven basket\textsuperscript{10}. The progressing understanding of the microstructure of the menisci gives an insight into stresses that they are under and provides a greater understanding of their function within the knee.

Figure 2-3: The left side shows a schematic representation of the fascicle structure in two different locations in the meniscus, with the corresponding optical projection tomography images on the right side (source: Andrews et al.\textsuperscript{10})
2.2 Meniscus Function

The tibiofemoral joint is the largest and most complex in the human body. Both of the semi-circular bony condyles of the femur rest in an incongruent manner on the mostly flat tibial plateau. The concave upper surface of the menisci and flat lower surface increase the congruency of the articulations. Menisci are found in all mammals, although there is variation in their shape and attachments\textsuperscript{192}. It is generally accepted that the primary role of the menisci is load distribution\textsuperscript{83, 162, 240}. In the loaded knee, the lateral meniscus transmits seventy per cent and the medial meniscus fifty per cent of the load through the knee. Biomechanical studies have shown that meniscectomy decreases the tibiofemoral contact area by fifty to seventy-five per cent and increases the peak contact pressure by 200 to 300 per cent\textsuperscript{22, 184, 277}. Figure 2-4 illustrates the relative differences in contact area and pressures with and without a meniscus. The menisci have also been shown to provide secondary constraint to the knee\textsuperscript{171, 172, 179}. Further roles have been proposed, including joint lubrication\textsuperscript{224} and proprioception\textsuperscript{192}. Shock absorption is commonly stated as a function of the menisci, although there is little evidence to support this and arguably some refuting this hypothesis\textsuperscript{9}. 
2.3 Meniscal Tears: Incidence, Classification and Treatment

Meniscal tears are common; the yearly incidence of operated meniscal tears has been estimated at 90 and 42 per 100 000 for males and females respectively, based on a study in a suburban area of Copenhagen, Denmark. They also found that the tear was associated with an acute traumatic event in seventy-seven and sixty-four per cent of cases in males and females respectively. Bucket handle tears were most common in males (thirty-five per cent), whereas peripheral detachments were most common in females (forty-one per cent). In an historical study based on a population in New York, USA, Baker et al. estimated a yearly meniscectomy incidence of 61 per 100 000 population. They also found that it was more common in males (three to one males to females respectively) and medial meniscectomy was more common (eighty-one to nineteen per cent medial to lateral respectively). More recently, a review of NHS knee operations found that the yearly incidence of meniscus-related operations was 35 per 100 000 population. These differences may reflect the...
changes in management of meniscal tears over time, as well as geographical differences in treatment.

The treatment of meniscal tears has evolved considerably throughout orthopaedic history. In 1897 the meniscus was described as a remnant of leg muscle that served no biomechanical function. In 1889 Annandale, who had previously reported a meniscal repair, advocated complete excision of tears, which became standard practice for the next eighty years. In 1948 Fairbank was the first to associate OA changes on plain radiographs with meniscectomy. However, total meniscectomy continued to be standard treatment for meniscal tears until a number of studies reported high rates of OA following total meniscectomy, in long term case series. These studies, combined with the rise of arthroscopic surgery, created a paradigm shift in practice to meniscal preserving surgery (partial meniscectomy and meniscal repair) whenever possible.

Meniscal tears may be broadly categorised as traumatic or degenerative. Traumatic tears have an acute onset and are often caused by a sporting injury. Figure 2-5 shows common tear patterns of the meniscus. Longitudinal tears (in line with the circumferential collagen fibres) are as a result of axial loading and rotating of the femoral condyles. This tear pattern can result in a bucket handle tear that can dislocate into the knee, causing knee locking. Traumatic radial and root tears can also occur, which can cause extrusion and potentially defunction the meniscus. Symptomatic traumatic meniscal tears are usually treated with either meniscal repair or meniscectomy. Meniscal repair has been shown to improve PROMs, when compared to meniscectomy, in a recent meta-analysis. However it is not always possible to repair a meniscal tear; a delayed presentation and certain tear patterns can
reduce the chance of being able to perform a repair. There is also a high failure rate of meniscal repairs, with one meta-analysis reporting a pooled failure rate of twenty-three per cent at five years post-operatively\textsuperscript{200}. These patients then often have a meniscectomy.

![Different meniscus tears patterns](www.aidmymeniscus.com)

Figure 2-5: Different meniscus tears patterns (source: www.aidmymeniscus.com)

Patients with degenerative meniscal tears are usually older and do not usually describe a single traumatic event. The tear is usually complex (more than one tear pattern), and fibrillation of the meniscus is commonly seen at arthroscopy. Degenerative tears are not normally repairable and partial meniscectomy has commonly been performed if patients are symptomatic\textsuperscript{50}. However a number of methodologically strong studies have found no significant benefit of this approach to the general population. Herrlin et al. performed a RCT comparing meniscectomy and physiotherapy to physiotherapy alone in patients with a non-traumatic medial meniscal tear, finding no significant differences in outcomes\textsuperscript{127}. Katz et al. performed a RCT comparing partial meniscectomy and physiotherapy to physiotherapy alone in patients over forty-five years of age with a meniscal tear and knee OA, finding no benefit of meniscectomy\textsuperscript{146}. However, there was a high
crossover to the surgical group, with those patients having a low patient reported outcome scores before crossover. Sihvonen et al. also performed a RCT comparing partial meniscectomy with sham surgery in patients with a degenerate (non-traumatic) medial meniscal tear in the absence of knee OA, finding no benefit of partial meniscectomy over sham surgery\textsuperscript{245}.

It has been shown that degenerative meniscal tears are common incidental findings in older people. Englund et al. found that over fifty per cent of men between seventy and ninety years selected from a random sample of ambulatory people had meniscal tears\textsuperscript{94}. Bhattacharya et al. looked at the prevalence of meniscal tears in a sample of older patients (mean age sixty-six years) with symptomatic knee OA, and aged matched controls, finding ninety-one compared to seventy-six per cent of patients had a tear respectively. It is likely that degenerative meniscal tears are part of the OA disease process. Englund et al. clinically and radiographically reviewed 317 patients that had a meniscal resection between fifteen and twenty-two years previously\textsuperscript{93, 96}. They found that a degenerative type meniscal tear and obesity were the most strongly associated risk factors for symptomatic and radiographic knee OA. They also found that hand OA was associated with an increased likelihood of knee OA following meniscal resection. They concluded that surgical resection may only remove the evidence of early OA, rather than address it.

### 2.4 Knee Osteoarthritis and Meniscectomy

OA is a clinical syndrome of joint pain with associated functional limitation and reduced quality of life. It is the outcome of a range of disorders in which mechanical factors play a central role, resulting in the structural and functional failure of the
whole joint. It is the biggest cause of musculoskeletal disability in the developed world and in the top ten of causes of disease burden in high income countries. The knee is one of the most commonly affected joints and more than 250 million people worldwide may suffer from it. The 1986 classification, developed by the American College of Rheumatology, is often used to standardise the diagnosis of OA in a research setting. More recent evidence-based recommendations refer specifically to the diagnosis of knee OA. These gave recommendations to the aid diagnosis of OA, considering risk factors, symptoms, signs and radiographic features.

Meniscectomy is a strong predictor of future knee OA. In 1948 Fairbank radiologically reviewed 107 patients at three to fourteen months following meniscectomy, commonly finding flattening of the femoral condyle and narrowing of the joint space in the affected compartment. Since then there have been numerous studies reporting clinical and radiological changes following meniscectomy. Roos et al. compared 123 patients that had open meniscectomy for an isolated tear to age and sex matched controls twenty-one years after surgery, finding a relative risk of fourteen (95% CI 3.5 to 121.2) for definite radiological OA. Hunter reviewed 257 patients with symptomatic knee OA over thirty months, finding a strong association between meniscal damage and cartilage loss. The same group also found that loss of meniscal coverage and height was associated with cartilage loss. Papalia et al. performed a systematic review looking at risk factors for OA after the surgical management of meniscal tears, in studies with a follow up of between five and thirty years. They identified 4642 patients in thirty-two studies, with a mean prevalence of knee OA of fifty-four per cent (range sixteen to ninety-three per cent). When comparing radiological evidence of OA, the mean prevalence in the
operated group was forty per cent compared to the contralateral (control) knee of six per cent. They also found a higher incidence of OA with lateral compared to medial meniscectomies and with total compared to partial meniscectomies. They concluded that there was a strong association between meniscectomy (medial or lateral) and OA. One study looked specifically at isolated traumatic meniscal tears, finding that the mean time from injury to first radiological signs of OA was ten years for the study group overall, or fifteen years in the age group seventeen to thirty\textsuperscript{229}. Salata et al. also performed a systematic review of outcomes following meniscectomy, finding that total meniscectomy, removal of the peripheral rim and lateral meniscectomy were all predictors of a poor clinical and radiological outcome\textsuperscript{236}. Englund et al. looked specifically at patients with meniscal damage that had not had surgery to identify whether meniscal damage was a risk factor for OA, independently of meniscectomy\textsuperscript{95}. They performed a case control study over a thirty month period, finding a odds ratio of six for developing OA if meniscal damage was present, compared to no meniscal damage. They concluded that meniscal damage by itself (i.e. without associated surgery) is a potent risk factor for developing OA.

These clinical studies provide evidence of a strong and consistent association between meniscal damage and OA. It is thought that damage to the meniscus causes changes to the biomechanical and therefore biochemical environment of the knee, which results in OA initiation and progression in susceptible patients\textsuperscript{183}. A number of studies have shown the biomechanical changes following meniscectomy. Krause was the first to show an increased stress on the knee joint following meniscectomy in a study on human cadavers\textsuperscript{162}. Baratz et al. performed a study, also on human cadavers, showing that total meniscectomy decreased tibiofemoral contact area by seventy-five per cent and increased peak contact stresses by 235 per cent\textsuperscript{22}. They
also found that peak contact stresses increased in proportion to the amount of meniscus removed. Paletta et al. also found similar results, with contact area decreasing by forty-five to fifty per cent and peak contact stresses increasing to between 235 and 335 per cent following total lateral meniscectomy\textsuperscript{212}. More recent studies have been able to show the local biomechanical changes to the articular cartilage and knee joint following meniscectomy. Song et al. performed a MRI study on sheep where they cyclically loaded sheep knees at a physiologic magnitude and frequency over two days, taking multiple images\textsuperscript{249}. They found that meniscectomy accelerated articular cartilage deformation during loading and that it remains chronically deformed and dehydrated on unloading, when compared to the normal knee. They hypothesised that central fibrillation of the articular cartilage may be started by the direct strain induced damage to the articular cartilage matrix, or the chronic changes in tissue hydration. Haemer et al. used the images in the study by Song et al. to create a finite element analysis model\textsuperscript{118}. They found a significantly increased strain in the articular cartilage and subchondral bone centrally in the knee. These increased strains were close to the reported failure limits for these tissues, including the surface zone of the articular cartilage. They hypothesised that this could lead to cartilage fibrillation and eventual breakdown. Peripherally, they found a significant loss of articular fluid pressurisation, which is thought to have a negative effect of cartilage maintenance. This loss of articular cartilage hydrostatic pressure may allow capillary invasion with subsequent endochondral ossification and osteophyte formation\textsuperscript{56}. These changes in the articular cartilage have also been seen after partial meniscectomy\textsuperscript{147}.

Evidence of joint degeneration following meniscectomy has also been reported in animal studies, with macroscopic, histological and biochemical changes. Articular
cartilage fibrillation, swelling, fissures and cleaved type two collagen have been seen following meniscectomy in a number of animal studies\textsuperscript{123, 164}. Lanzer and Komenda reported a loss of proteoglycans in the menisectomised knee\textsuperscript{164}. Young et al. used a sheep model to evaluate proteoglycan four levels and regulation following meniscectomy\textsuperscript{293}. Proteoglycan four is thought to be involved in joint lubrication and is present in the superficial zones of the articular cartilage of the normal knee. They found that following meniscectomy and the onset of early OA, proteoglycan four was lost from the superficial zones as well as a reduction in its expression from chondrocytes. Oakley et al. performed medial meniscectomies in sheep and observed the macroscopic and biochemical changes\textsuperscript{210}. They reported gross structural damage including cartilage softening and fibrillation as well as proteoglycan loss throughout the joint, with the greatest severity being closest to the meniscectomy site. They suggested that the observed changes pointed to biochemical and cytokine mediated responses, in addition to a change in the biomechanical environment. Appleyard et al. observed the variable responses in different regions of knee articular cartilage in response to meniscectomy, in a sheep model\textsuperscript{13}. They found that the entire articular cartilage of the lateral tibial plateau underwent degenerative changes. They also found that the joint margins became biomechanically softer than normal cartilage, which they hypothesised would undergo degeneration and progression of joint OA.

2.5 Meniscal Allograft Transplantation: History, Development and Clinical Outcomes

In response to reports of the clinical consequences of meniscectomy, meniscal replacement began to emerge in the 1980’s. Canham and Stanish reported the successful implantation of medial meniscal allografts in dogs, showing for the first time that a completely detached meniscus could be implanted successfully\textsuperscript{55}. They
also showed that the preservation technique was important; the tissue culture preservation group did considerably better than the gluteraldehyde group. In 1989 Milachowski, Weismeier and Wirth reported a series of meniscal allograft transplantations in thirty sheep and then twenty-two patients. This group performed the first human detached meniscal allograft transplantation in May 1984. They used two types of graft preservation: Deep frozen and lyophilised, reporting that the deep frozen ones had better outcomes. They concluded that meniscal allograft transplantation was a reasonable procedure and that they observed no adverse immunological reactions. Figure 2-6 shows arthroscopic images of a modern meniscal allograft transplant in the knee.

![Meniscal allograft transplant in a right lateral compartment of the knee at time zero (left) and at seven months (right)](image)

Figure 2-6: Meniscal allograft transplant in a right lateral compartment of the knee at time zero (left) and at seven months (right)

Other attempts have been made to substitute the meniscus, but with limited success. Kohn et al. attempted to use tendon autograft as a substitute, but this was found to be weaker than a native meniscus. Attempts to use a fat pad autograft were also unsuccessful as although it had the macroscopic appearance of a meniscus by six months, it had degenerated by one year and did not prevent OA changes. These results led to a shift towards meniscal allograft surgery.
Since the first reported human meniscal transplantation, there have been numerous case series reported in the literature.\textsuperscript{3, 35, 53, 60, 117, 165, 274} It is difficult to get an accurate estimate of the total number of transplantations performed worldwide as only a small percentage of case series are reported in the literature.\textsuperscript{91} In 2003 it was estimated that over 4000 transplantations had been performed in the USA alone, with a yearly rate approaching 800.\textsuperscript{243} In a consensus meeting amongst Danish surgeons, it was estimated that the yearly need for meniscal allograft transplantations in Denmark was between ten and fifty, in their population of five million.\textsuperscript{19} Although not directly comparable, extrapolating these figures would give a yearly need for between 126 and 630 in the UK and between 628 and 3139 in the USA. Despite this, there have been no RCTs of meniscal allograft transplantation performed. Therefore, the best evidence for the efficacy and controversies in meniscal transplant surgery come from systematic reviews of case series.

In 2007 Lubowitz et al. provided an overview of meniscal allograft transplantation, highlighting many dilemmas involving the treatment of symptomatic meniscal deficient patients.\textsuperscript{175} Nevertheless they concluded that meniscal allograft transplantation may reliably result in pain relief and increased function in the short and medium term. These conclusions were echoed two years later in a further systematic review.\textsuperscript{76} In 2011 (search performed in January 2010) a comprehensive systematic review, with limited data pooling was performed.\textsuperscript{91} They reported on the results of 1136 grafts across forty-four case series. Pooling the Lysholm scores (score 0 to 100, with 100 being the best), they found an improvement from forty-four pre-operatively to seventy-seven at final follow up (mean follow up 4.6 years). They concluded that the procedure was safe, reliable and that it should not be considered
experimental surgery. However, there were no randomised or other comparative studies reported. More recently, a systematic review focussing on long term outcomes after meniscal allograft transplantation found that improvements in clinical scores were maintained in the long term\textsuperscript{167}. The authors concluded that the procedure was effective at reducing symptoms and improving knee function in the long term. Since the publication of these systematic reviews, there have been a number of new studies reporting their results\textsuperscript{3, 37, 59, 60, 79, 143, 154, 156, 158, 170, 178, 238, 252, 295}. These studies report either longer term follow up or results from more recent surgery. A systematic review was needed to update the literature, both in terms of clinical outcome and to identify any trend changes amongst surgeons performing meniscal allograft transplantation. Trend changes were considered to be highly likely because there were many areas of controversy in meniscal transplantation, for example patient selection, graft type and surgical technique.

2.6 How Might Meniscal Allograft Transplantation Work?

As shown, there is evidence of a sustained improvement in PROMs following meniscal allograft transplantation, but it is important to understand how this might be caused. Clinically, OA may be defined as joint pain with varying levels of functional limitation and a reduced quality of life\textsuperscript{204}. Pathologically, it may be characterised by the failure of the repair process of damaged cartilage due to biomechanical and biochemical changes in the joint\textsuperscript{36}. This results in localised loss of cartilage, remodelling of adjacent bone and inflammation. NICE have acknowledged that structural changes in the joint are more closely linked to symptoms than previously thought and that interventions altering the joint structure could be expected to deliver symptomatic relief as well as delaying OA progression\textsuperscript{204}. It has been shown that
meniscectomy adversely alters the biomechanical and biochemical environment of
the knee and this translates to a high rate of OA in affected patients. The
pathogenesis of OA is not fully understood but abnormal loading patterns are
thought to result in focal excessive mechanical stresses of the joint surfaces\textsuperscript{40, 221}. This results in cumulative tissue micro-damage and re-modelling and is a source of pain\textsuperscript{281}. It has been shown that reducing joint or compartment forces improves pain and other symptoms in patients with OA\textsuperscript{65, 103, 190}. Patients that undergo meniscal allograft transplantation have usage related knee pain (the primary indication for surgery) often with functional limitation and radiographic features of joint disease\textsuperscript{91}. These symptoms (even without radiographic features) meet the criteria for the diagnosis of knee OA, especially in the presence of risk factors for OA (knee injury and meniscectomy), using the EULAR evidence based recommendations\textsuperscript{296}. It is thought that meniscal allograft transplantation restores the biomechanical environment closely to that of the pre-injury knee, thus reducing excessive and abnormal joint forces. This may then result in a symptomatic improvement and reduced or delayed progression of OA. Therefore, evidence that a meniscal allograft improves the knee biomechanics is vital to the scientific plausibility that it could be an effective intervention.

A number of biomechanical studies have been performed to compare the load
sharing ability of meniscal allografts with the native meniscus, as well as a knee with no meniscus. In 1997, Paletta et al. used young human cadaveric knees to test the
total contact area and peak contact pressure changes following meniscectomy and
then subsequent allograft transplantation\textsuperscript{212}. They found that the total contact area
decreased by forty-five to fifty per cent following meniscectomy and then increased
by forty-two to sixty-five per cent after allograft transplantation (compared with
meniscectomy scores) at all tested knee flexion angles. They also found that peak contact pressures increased by 235 to 335 per cent following meniscectomy, and were decreased by fifty-five to sixty-five per cent after allograft transplantation (compared with meniscectomy scores) at all tested knee flexion angles. The improvements following transplantation however did not reach the level of the native knee. These results were similar to another study historic study, whilst a further study found that normal biomechanics were restored at low compressive loads, but not high. Dienst et al. compared contact pressures with under and oversized menisci, finding that oversized menisci allowed greater forces across the articular cartilage whilst undersized menisci restored normal forces across the articular cartilage but resulted in higher forces across the meniscus. They reported that two undersized menisci failed, potentially showing the importance of appropriately sized grafts in meniscal allograft transplantation. More recently, McDermott et al. reported a human cadaveric study comparing the native knee with a bone plug fixation, an all suture allograft fixation and meniscectomy. They found that both the bone plug technique (p=0.0029) and the all suture technique (p=0.0199) of allograft fixation significantly reduced peak contact pressures, compared to meniscectomy. They also found that the peak contact pressures of the knees with meniscal allografts (either technique) were not significantly different to the native knee. Based on their study, they hypothesised that meniscal allograft transplantation was likely to have a chondroprotective effect.

All these studies reported an improvement in contact biomechanics following meniscal allograft transplantation. The majority of studies showed that normal biomechanics could not be restored, but the most recent study, which used techniques that most closely match the most used modern transplantation techniques
showed no significant difference between the transplanted and native knee. These results support the hypothesis that the meniscal allograft functions in a similar way to a native meniscus. However there are limitations of the application of these results to patients. These studies were cadaveric and cannot simulate living conditions. In living patients, the meniscus is subject to a different immunological, biochemical and biomechanical environment. Therefore at best, these results only really apply to a newly implanted meniscal allograft. There are also differences in living loading patterns that cannot be biomechanically simulated. Also, for logistic reasons the surgical technique used in the cadaveric studies was very different to that used in living patients. In the study that best replicated that surgical techniques used today, an open technique with lateral collateral ligament (LCL) detachment and capsular opening was performed. Whilst the LCL was repaired, the capsule was left open. Finally, the cadaveric specimens were usually older than patients that usually undergo meniscal transplantation. The effect of these limitations can only be speculated upon, but the overall results do increase the scientific plausibility that meniscal allograft transplantation can improve the biomechanical environment of the knee.

2.7 Is Meniscal Allograft Transplantation Chondroprotective?

Animal models have been used extensively to record changes in the knee following meniscectomy and was further used to show that meniscal allograft transplantation could be successfully performed. Since then, it has been used to see whether meniscal transplantation is chondroprotective. Szomor et al. compared four groups using sheep: sham operation, meniscal allograft, meniscal autograft and meniscectomy. At four months they compared the knee articular cartilage...
macroscopically and microscopically, finding significant protection of the articular cartilage in the allograft and autograft groups, compared to the meniscectomy group. They did not see a noticeable difference between the allograft and autograft groups. Kelly et al. performed a similar study, with a proportion of sheep being assessed at twelve months, as well as two and four months. They also used MRI T2 mapping to assess the articular cartilage. They found that the meniscal allograft group showed a significant decrease in articular cartilage degeneration compared to the meniscectomy group. When comparing the allograft to the control group, there was no difference at two months, but by four months the allograft group had evidence of more cartilage degeneration.

These results suggest that in animal models meniscal allograft transplantation may be chondroprotective, but does not completely reverse the effects of meniscectomy. This evidence builds on the biomechanical studies that show meniscal allograft transplantation improves contact mechanics. Whilst these results support the chondroprotective hypothesis, direct inferences cannot be drawn between animal and human studies. There are many reasons that the application of animal studies to human patients is severely limited: Animal knees are different in shape, movement and function; the surgical technique is different; the pathology of traumatic meniscal tears cannot be accurately be recreated and the timeline is short. As well as this, there have been strong doubts raised about the design and quality of animal studies.

Authors of meniscal allograft transplantation case series often comment on the likely chondroprotective benefit, but the evidence to support this is in humans limited and circumstantial. Whilst a few studies have reported radiological outcomes following
meniscal allograft transplantation, they largely lack an adequate control group and no RCTs have been performed\textsuperscript{79, 154, 266, 274}. Prior to this thesis, there had been no systematic reviews focussed on addressing whether meniscal allograft transplantation is chondroprotective.

Hergan et al. stated that the most important question was whether meniscal allograft transplantation can preserve the knee articular cartilage\textsuperscript{126}. Further, they state ‘Without a prospective, randomized [sic] trial comparing MAT [meniscal allograft transplantation] in a meniscectomized [sic] knee with a control group, we will continue to lack an evidence-based answer for our patients.’

### 2.8 Meniscal Substitutes and Tissue Engineering

Whilst there has been renewed interest in alternative treatments for patients with a symptomatic meniscal deficient knee, there have been no clear breakthroughs in clinical studies. A device called Collagen Meniscus Implant (also known as Menaflex, Regen Biologics, Hackensack, NJ) is a collagen scaffold, designed to encourage new meniscus growth. It is used to treat partial meniscal defects and although case series show improvements in clinical scores, a RCT showed it to be no better than partial medial meniscectomy\textsuperscript{225}. Biopsies also showed that the new tissue formed was a hybrid repair tissue, rather than meniscus fibrocartilage. A polyurethane implant, Actifit, (Orteq, London, UK) is also used to treat partial meniscal defects, but is not yet proven (Figure 2-7). In 2012 NICE published a guideline on partial meniscal replacement using a biodegradable scaffold\textsuperscript{202}. They stated that the evidence for scaffolds over standard surgery was limited and the
procedure should only be carried out with special arrangements for clinical governance, consent and research.

![Actifit Scaffolds](source: Orteq Sports Medicine)

There has been an increased interest in tissue engineering and the use of stem cells with polymeric scaffolds in pre-clinical studies\textsuperscript{216}. These studies are interesting and may be successful future therapies, but are currently in the early stages of development. Contrastingly, meniscal allograft transplantation is an established treatment for patients with a symptomatic meniscal deficient knee and is available on the NHS without restriction.

### 2.9 Physiotherapy: Definition and Clinical Outcomes

Physiotherapy aims to restore movement and function to people affected by illness, injury or disability through physical treatments\textsuperscript{203}. Interventions that a physiotherapist may use include movement and exercise, manual therapy, education and advice. Physiotherapy has a long history and is widely used on the NHS as a primary intervention, an adjunct to other interventions and for rehabilitation following surgery. Physiotherapy used for musculoskeletal conditions can aim to
improve strength, co-ordination, balance, proprioception, flexibility and aerobic capacity. Physiotherapy usually has a number of advantages over drug and surgical interventions as it is safe, inexpensive and is patient-driven to achieve long term self management.

Physiotherapy has a strong evidence base for use in patients with knee OA. Uthman et al. published a sequential meta-analysis in the British Medical Journal showing that by 2002 there was enough evidence to show a clear benefit of exercise compared to no exercise for pain and functional improvement in patients with lower limb OA. They also concluded that further evidence was unlikely to overturn the results. Of the sixty RCTs, forty-four were involving the knee alone and fourteen included mixed lower limb joints including the knee (two were hip alone). They showed that there was evidence for strengthening, flexibility and aerobic exercises, as well as combinations of the three. In a recent update, the authors of the Cochrane review on exercise for OA of the knee reported similar findings. They concluded that there was high quality evidence for an improvement in pain for at least two to six months following the cessation of exercise interventions and moderate quality evidence for functional improvement; the magnitude of effect was reported to be similar to non-steroidal anti-inflammatory drugs (NSAIDs). In 2014, NICE recommended exercise as a core treatment for people with OA, in their OA care guideline. Specifically, they recommended local muscle strengthening and general aerobic fitness, which could be tailored according to each individual’s needs. A further RCT compared two different types of physiotherapy (neuromuscular training and quadriceps strengthening) in people with moderate to severe OA. They found significant improvements in pain and function in both groups but no between group differences.
Physiotherapy has also been advocated for rehabilitation following meniscectomy. In 2013, a systematic review found eighteen RCTs comparing post-operative rehabilitation to controls or other rehabilitation programmes. In their subsequent meta-analysis of six suitable studies, they found a statistically significant improvement in patient reported knee function and knee range of motion in participants that had outpatient physiotherapy and a home exercise programme, compared to a home exercise programme alone\textsuperscript{80}.

2.10 How Might Physiotherapy Work?

One of the common features of a structured physiotherapy programme is strength training (sometimes called resistance training). Patients with knee pain and OA have been shown to have lower limb weakness, compared to controls\textsuperscript{21, 209}. It has also been shown that quadriceps strength is reduced following partial meniscectomy, which is still not fully recovered at four years following surgery\textsuperscript{99}. It has been proposed that lower limb muscle weakness reduces the ability to decelerate leg movement and is less able to absorb joint forces, with resulting pain, reduced function and a resulting negative effect on articular cartilage\textsuperscript{31, 33, 82}. The findings by Ding et al. supported this hypothesis as they found that reduced lower limb strength was independently associated with femoral cartilage loss\textsuperscript{82}. It has also been shown that physiotherapy (with incorporated strength training) improves strength and endurance in people with OA\textsuperscript{104, 142} and people with a history of meniscectomy\textsuperscript{98}. These studies in people with OA also found a corresponding improvement in pain and function.
An integral part of physiotherapy is the encouragement of a return (or start) to exercise. This may improve functional and quality of life scores due to the general benefits of exercise to fitness, function and health-related quality of life\textsuperscript{28, 29, 193}.

2.11 Is Physiotherapy Chondroprotective?

Despite a large amount of evidence to show an improvement in pain and function for people with OA, there is very little evidence to determine whether it may be chondroprotective.

Thorstensson et al. used the surrogate outcome measure knee adduction moment (KAM) to determine whether an eight week exercise programme had the potential to reduce the risk of OA, in a pilot study\textsuperscript{259}. They compared peak KAM during a one-leg rise in the exercised limb to the contralateral limb, finding a statistically significant reduction in the exercised knee. KAM is determined from gait analysis and reflects medio-lateral joint distribution. It has been shown to correlate well with medial tibiofemoral contact force\textsuperscript{163} and is associated with OA progression\textsuperscript{195}. However these results have been challenged by other studies. One RCT compared neuromuscular rehabilitation to quadriceps strengthening in patients with medial tibiofemoral OA and varus alignment, finding similar improvements in pain and function between groups but no changes in KAM\textsuperscript{32}. In another RCT by the same lead author, hip strengthening was compared to no intervention in patients with medial tibiofemoral OA and varus alignment\textsuperscript{30}. They found pain, function and muscle strength were all improved in the intervention group, but no significant changes in KAM were observed. A further RCT supported these findings, finding no significant differences in KAM between patients that had a six month resistance training
intervention compared to a sham intervention, despite symptoms improving\textsuperscript{104}. This led the authors to conclude that the mechanism of action could be something other than improved joint loading.

Chapter five in this thesis specifically identified studies treating patients with a meniscal deficient knee and systematically appraised the evidence for whether physiotherapy may reduce the risk of OA in these patients.

\textbf{2.12 Summary}

The menisci are complex structures that are not fully understood. They have a variable microstructure, which is thought to reflect the different stresses (and functions) in different parts of the meniscus. The primary function of the meniscus is load distribution; the loss of a meniscus results in negative biochemical and biomechanical changes and is a strong predictor of future OA. Both meniscal allograft transplantation and physiotherapy are used to treat patients with symptomatic meniscal deficient knees.

Meniscal allograft transplantation has been used for over thirty years with multiple case series showing an improvement in PROMs. It is also scientifically plausible that it could reduce or delay the progression of OA. In chapters three and four, the literature was systematically reviewed to determine the current best evidence for whether meniscal allograft transplantation improves PROMs and reduces or delays the progression of OA respectively.
Physiotherapy has a strong evidence base for improving pain and function in patients with symptomatic OA of the knee and is recommended as a treatment by NICE\textsuperscript{204}. It is also a relatively safe treatment. It was therefore determined that physiotherapy was an appropriate comparator to meniscal allograft transplantation for the treatment of patients with a symptomatic meniscal deficient knee.

It is less clear whether physiotherapy can reduce or delay the progression of OA in patients with a history of meniscectomy. In chapter five, the literature was systematically appraised to determine whether there was evidence that physiotherapy is chondroprotective in patients with a history of meniscectomy.
3 Meniscal Allograft Transplantation in a Symptomatic Meniscal Deficient Knee: A Systematic Review

Declarations

The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Nicola MacKay.

This work has been published:


This work has been presented:

West Midlands Surgical Society Autumn Meeting, Good Hope Hospital UK, 2014.
A systematic review of meniscal allograft transplantation for the treatment of a
symptomatic post-meniscectomy knee. (Poster)

Funding body

This research was supported by Arthritis Research UK (grant number 20149).

3.1 Introduction

It was shown in chapter two that meniscal allograft transplantation was first
performed over thirty years ago and then since then there have been many cases
reported in the literature. It has been advocated for the treatment of post-
meniscectomy symptoms, which can consist of pain, swelling and loss of function.
In 2011 a systematic review and meta-analysis (search performed in January
2010) showed an improvement in symptoms and function but highlighted a lack of
good quality studies. Since then there have been a number of further studies, and
longer follow up of some older studies have been reported. The primary objective of
this study was to perform an updated systematic review of meniscal allograft
transplantation for the treatment of the symptomatic meniscal deficient knee, using
PROMs as the primary outcome measure. The secondary objective was to provide a
review of the indications, associated procedures, operative technique, rehabilitation,
failures, complications, radiological outcomes and graft healing. This was needed to
identify whether there had been changes in the major components of meniscal
allograft transplantation as a complex intervention. It also allowed a comparison
between common worldwide practice and local protocols. Ideally, they should be similar to allow a definitive evaluation to have high external validity. Deviations from common practice would need to be carefully considered before being implemented in the context of a definitive evaluation.

3.2 Materials and Methods

3.2.1 Quality of methodology
This study has been reported in accordance with the PRISMA statement for reporting systematic reviews\textsuperscript{173}. The protocol was published on PROSPERO, the York prospective register of systematic reviews prior to undertaking the searches (Appendix A).

3.2.2 Eligibility criteria

- **Study type**
  Any case series or clinical comparative study (including RCTs) written in the English language. Biomechanical studies, case reports and systematic reviews that did not contain new patient data were excluded

- **Participants**
  Any human of any age
• **Intervention**

Meniscal allograft transplantation using any allograft preserving method and any grafting type

Any rehabilitation regime post-operatively

• **Comparator**

If a comparator group existed, it had to be a reasonable alternative treatment to meniscal allograft transplantation or a difference in meniscal allograft transplantation methodology, for example different allograft fixation technique

• **Outcome measures**

A study had to include a PROM at a minimum of one year post-operatively for every patient. Commonly used PROMs included Lysholm, IKDC and Tegner activity index, but any other PROM was accepted

3.2.3 *Search strategy*

A search was undertaken for both published and unpublished studies. The design of the search strategy was sensitivity maximising in order to reduce the risk of missing eligible studies. The published search strategy was developed using a combination of keywords and ‘subject headings’, which were exploded to maximise the inclusion of potentially relevant studies. The search strategy for Medline (Ovid) (Table 3-1) was adapted for Embase (Ovid) and the Cochrane library (CENTRAL). The references of eligible studies and previous systematic reviews were searched for other potentially relevant studies. Unpublished studies were searched according to recommendations from a recent article published in the British Medical Journal\(^6\). The World Health
Organisation International Clinical Trials Registry Platform and Clinical Trials Registry were searched for on going or complete trials. The Web of Science was searched for conference proceedings.

Table 3-1: Search strategy for Ovid Medline (1946 to March week 3 2014), performed on the 2nd April 2014

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
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<td>exp Menisc*, Tibial/</td>
<td>6007</td>
</tr>
<tr>
<td>2</td>
<td>Menisc*.mp.</td>
<td>10957</td>
</tr>
<tr>
<td>3</td>
<td>(allograft* or transplant*).mp.</td>
<td>519356</td>
</tr>
<tr>
<td>4</td>
<td>1 or 2</td>
<td>10957</td>
</tr>
<tr>
<td>5</td>
<td>3 and 4</td>
<td>796</td>
</tr>
<tr>
<td>6</td>
<td>(case series or compar* or randomi* or clinical or trial*).mp.</td>
<td>6121278</td>
</tr>
<tr>
<td>7</td>
<td>5 and 6</td>
<td>469</td>
</tr>
<tr>
<td>8</td>
<td>limit 7 to (english language and humans)</td>
<td>338</td>
</tr>
</tbody>
</table>

3.2.4 Selection and appraisal method

Figure 3-1 and Figure 3-2 are flow diagrams of the selection processes for published and unpublished studies respectively. Results of the database searches were transferred into EndNote and duplicates were automatically discarded. Pre-defined criteria were used to assess the eligibility of the remaining studies from their title and abstract. The full papers of the remaining studies were then reviewed.

Data from eligible studies was extracted and studies that contained some or all of the same patients were grouped. In order to reduce the risk of duplicate publication bias\(^\text{138}\), the study with the longest mean follow up was included in the analysis, with the other studies cited in the references but excluded from further analysis.
Failures and complications were collected as reported by each study. If failures were not specifically defined, a failure was considered to be either the complete removal of the allograft, revision meniscal allograft transplantation or conversion to joint replacement. If complications were not defined, a complication was considered to be any reported adverse event that the patient experiences.

Figure 3-1: Flow diagram for the appraisal of published studies
3.3 Results

Of the forty-eight eligible studies, thirteen contained some or all of the same patients as other eligible studies and were excluded. Therefore there were 1332 patients (1374 knees) in thirty-five studies included in this systematic review (Table 3-2). There were no prospective controlled trials, randomised or otherwise, eligible for inclusion.
The earliest study recruited patients from 1984 and the last recruitment year from any study was 2010. The follow up range across all studies was from one to twenty years, with a mean of 5.1 years. The youngest and eldest patients were thirteen and sixty-nine years old respectively, with a mean age at the time of surgery across all studies of 33.7 years. Of the 1332 patients, 762 were male and 343 were female; the gender was not reported for 227 patients. There were 587 medial and 657 lateral allografts across all studies.
Table 3-2: Summary of included studies

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study type</th>
<th>Participants</th>
<th>PROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chalmers et al.</td>
<td>2013</td>
<td>Retrospective case series</td>
<td>13</td>
<td>Lysholm, IKDC,</td>
</tr>
<tr>
<td>Stone et al.</td>
<td>2013</td>
<td>Case series</td>
<td>68</td>
<td>IKDC, Tegner, WOMAC</td>
</tr>
<tr>
<td>Hardy et al.</td>
<td>2013</td>
<td>Retrospective case series</td>
<td>22</td>
<td>Lysholm, IKDC, KOOS</td>
</tr>
<tr>
<td>Abat et al.</td>
<td>2012</td>
<td>Parallel prospective case series</td>
<td>88</td>
<td>Lysholm</td>
</tr>
<tr>
<td>Binnet et al.</td>
<td>2012</td>
<td>Case series</td>
<td>4</td>
<td>Lysholm, Tegner</td>
</tr>
<tr>
<td>Carter</td>
<td>2012</td>
<td>Prospective case series</td>
<td>40</td>
<td>Lysholm, IKDC</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2012</td>
<td>Retrospective case series</td>
<td>106</td>
<td>Lysholm</td>
</tr>
<tr>
<td>Koh et al.</td>
<td>2012</td>
<td>Retrospective case series</td>
<td>99</td>
<td>Lysholm</td>
</tr>
<tr>
<td>Marcacci et al.</td>
<td>2012</td>
<td>Prospective case series</td>
<td>32</td>
<td>Lysholm, IKDC, Tegner</td>
</tr>
<tr>
<td>Saltzaman et al.</td>
<td>2012</td>
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<td>22</td>
<td>Lysholm, IKDC</td>
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<tr>
<td>Zhang et al.</td>
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<td>Lysholm</td>
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<td>Parallel prospective case series</td>
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<tr>
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<td>15</td>
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</tr>
<tr>
<td>Ha et al.</td>
<td>2010</td>
<td>Retrospective case series</td>
<td>36</td>
<td>Lysholm</td>
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<tr>
<td>LaPrade et al.</td>
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<td>34</td>
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<tr>
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<td>Case series</td>
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<td>29</td>
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<td>Case series</td>
<td>20</td>
<td>Lysholm, Tegner</td>
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<td>2006</td>
<td>Prospective case series</td>
<td>36</td>
<td>Lysholm, IKDC, Tegner</td>
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<tr>
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<td>2006</td>
<td>Retrospective case control</td>
<td>16</td>
<td>Lysholm, IKDC</td>
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<tr>
<td>Sekiya et al.</td>
<td>2006</td>
<td>Retrospective case series</td>
<td>25</td>
<td>Lysholm and IKDC follow up scores</td>
</tr>
<tr>
<td>Stone et al.</td>
<td>2006</td>
<td>Prospective case series</td>
<td>45</td>
<td>Self reported pain, activity and functioning</td>
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<td>Retrospective case series</td>
<td>28</td>
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<td>Retrospective case series</td>
<td>31</td>
<td>Lysholm</td>
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<tr>
<td>Ryu et al.</td>
<td>2002</td>
<td>Retrospective case series</td>
<td>25</td>
<td>Lysholm, Tegner</td>
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<tr>
<td>Wirth et al.</td>
<td>2002</td>
<td>Prospective case series with retrospective control groups</td>
<td>21</td>
<td>Tegner</td>
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<td>Rath et al.</td>
<td>2001</td>
<td>Prospective case series</td>
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<td>SF36</td>
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<td>Stollsteimer et al.</td>
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<td>Prospective case series</td>
<td>22</td>
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<td>Case series</td>
<td>63</td>
<td>Tegner, Fulkerson</td>
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<tr>
<td>Noyes et al.</td>
<td>1995</td>
<td>Case series</td>
<td>82</td>
<td>ADLs and pain</td>
</tr>
</tbody>
</table>
3.3.1 Patient reported outcome measures

The Lysholm score is graded from 0 (worst) to 100 (best) and was designed to assess outcomes following knee ligament surgery\textsuperscript{176}. It was the most commonly used PROM, being used in 25 studies. The mean pre-operative score was 55.7 and at final follow up the mean score was 81.3 (Figure 3-3). A poor score is considered to be under 65, fair 65-83, good 84-90 and excellent over 90. Using these measures, the average pre-operative score was easily within the ‘poor’ range. At final follow up the score was ‘fair’, although close to the ‘good’ range.

![Graph showing follow up Lysholm scores. The y axis is ordered by length of follow up. Number of allografts in study (n). Jang a = Pollard size matched group, b = modified method of size matching. Koh a = medial allograft group, b = lateral. Abat a = suture only group, b = bone fixation group.](image-url)

Figure 3-3: Follow up Lysholm scores. The y axis is ordered by length of follow up. Number of allografts in study (n). Jang a = Pollard size matched group, b = modified method of size matching. Koh a = medial allograft group, b = lateral. Abat a = suture only group, b = bone fixation group.

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\textsuperscript{176} References are provided in the full document.
The International Knee Documentation Committee (IKDC) subjective knee form evaluates symptoms and function in activities of daily living\textsuperscript{128}. It was initially designed to assess ligament disruption in the knee but has been shown to be useful for a broad range of knee pathologies\textsuperscript{122}. The range is from 0 (worst) and 100 (best). It was used in twelve studies; pre-operative and final follow up mean scores were 47.8 and 70 respectively (Figure 3-4). These scores are consistent with the improvement seen in Lysholm scores, as pre-operative scores were very low for a young patient population and final follow up scores were significantly better but not near the best possible score.

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{ikdc_scores.png}
\caption{Follow up IKDC scores. The y axis is ordered by length of follow up. Number of allografts in study (n).}
\end{figure}
\end{center}
The Tegner activity level scale is a single score from 0 (worst) to 10 (best) that denotes the highest activity level that the patient performs\textsuperscript{257}. A level 0 would mean the patient is on sick leave due to knee problems, and 10 would mean the patient participates in national level football or rugby. It was used in 11 studies with pre-operative and final follow up mean scores of 3.1 and 4.7 respectively (Figure 3-5). An activity level 3 is light work, 4 is moderately heavy work and 5 is heavy work, recreational jogging or competitive cycling. Levels 6 to 10 are recreational and competitive sports such as running, football and tennis. Based on the mean change between pre-operative and final follow up, there was a significant increase in activity levels.

Figure 3-5: Follow up Tegner scores. The y axis is ordered by length of follow up. Number of allografts in study (n).

Some studies used other PROMs such as the Fulkerson questionnaire\textsuperscript{53}, Short Form Health Survey (SF-36)\textsuperscript{222}, Hospital for Special Surgery (HSS)\textsuperscript{275}, Knee Injury and
Osteoarthritis Outcome Score (KOOS)\textsuperscript{124}, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)\textsuperscript{252}, as well as pain and activities of daily living scores\textsuperscript{205}. These showed improvements broadly in line with the more commonly used PROMs (results not shown).

\subsection*{3.3.2 Indications}

The most frequently reported indications for meniscal allograft transplantation were a symptomatic (pain, swelling or stiffness) knee and a previous total or near total meniscectomy. Most studies did not define the extent of meniscectomy, although Farr et al. said that it should be within three millimetres of the posterior horn. The level or type of symptoms were not usually defined and only some studies required the symptoms to be present specifically on the same side of the knee as the meniscectomy. Most studies included an upper age limit or described eligible patients as ‘young’. Only two studies included patients over fifty-five years of age\textsuperscript{156, 253}. Severe cartilage damage or osteoarthritis were exclusion criteria for a significant number of studies\textsuperscript{68, 116, 131, 143, 156, 178, 222, 234, 242, 295}, although were not for a limited number of other studies\textsuperscript{35, 53, 109}. Normal alignment and/or a stable knee was a common requirement; this could usually be corrected intraoperatively\textsuperscript{68, 116, 143, 156, 178, 222, 233, 242}.

\subsection*{3.3.3 Graft type}

The graft type was known in 1186 allografts. There were 796 fresh frozen, 269 cryopreserved, 100 fresh and 21 lyophilized allografts used across all studies. Although cryopreserved and fresh frozen grafts were used in roughly equal numbers until 2010\textsuperscript{91}, all studies published since then have used fresh frozen grafts, with the
exception of a long term follow up case series of four grafts. This represents a significant change in practice from the previously reported systematic review by Elattar et al. Grafts in earlier studies were irradiated but this practice has now stopped.

3.3.4 Operative technique

The surgical technique was described in 1263 allografts. Earlier studies used an open technique, with collateral ligament detachment or joint distraction. Once an arthroscopic assisted technique had been pioneered, it quickly became the technique of choice. Bone bridge or plug fixation for the meniscal roots was the most common method, being used in 904 allografts (across twenty-six studies) whereas an all suture technique was used in 359 allografts (across thirteen studies). One study found more cases of major extrusion on MRI with their soft tissue fixation than their bone plug fixation, although PROMs were not significantly different between the groups.

3.3.5 Associated procedures

Other knee procedures performed at the time of meniscal allograft transplantation were common. The inclusion criteria for a number of studies were a stable knee with normal alignment, which was often corrected intra-operatively with an osteotomy and/or ACL reconstruction. Other commonly reported procedures included articular cartilage repair procedures including autologous chondrocyte implantation (ACI) and microfracture. Only 243 allografts were clearly performed as isolated procedures, although this is likely to be higher as reporting of isolated meniscal allograft transplantation in some studies was either not clear or not described. In a
number of studies, all patients had associated procedures: ACI or osteochondral allograft transplantation \(^{234}\), ACL reconstruction \(^{241}\), chondroplasty and scar debridement \(^{253}\), ACL reconstruction and/or medial collateral ligament advancement \(^{287}\).

3.3.6 Rehabilitation

Although there were variations in post-operative rehabilitation, most studies reported a post-operative period of either partial or non-weight bearing and a restriction on flexion from zero degrees to between sixty and ninety degrees. Most studies had allowed full weight bearing by six weeks, with a gradual progression to running by three to six months. Return to full pivoting/cutting sports was controversial with some studies recommending lifelong limits \(^{116, 222, 241, 242, 291}\). However, it was more common to allow return to full sports, usually after six to twelve months \(^{6, 37, 60, 109, 143, 178, 233, 250, 252, 275}\). Stone et al. reported a case series of patients with a pre-injury Tegner activity index score of eight or greater \(^{252}\). They found no correlation with post-operative sporting level and failure, concluding that patients with high pre-injury sporting demands can return to sports after surgery.

3.3.7 Failures and complications

Failures were variably defined. One study defined failure as poor functional scores linked to poor appearance of the meniscus \(^{275}\), whilst another considered no improvement in pain or a poor Lysholm score to be a failure \(^{131}\). The most common definition of failure was conversion to a joint replacement or excision of the allograft. There were six studies (198 allografts) that did not show evidence of reporting possible failures \(^{37, 158, 234, 241, 242, 291}\). Therefore there were a total of 128
failures in 1174 allografts implanted at a mean of 4.8 years across included studies (10.9% failure rate). The study with the highest number of failures had 29 out of 96 allografts at two year follow up. They found no significant difference in mean activity of daily living and pain scores between failures and healed grafts.

Complications were varied and included infection, synovitis, meniscal tears and partial meniscal detachments. Complications ascribed to concomitant procedures such as osteotomy or ACL reconstruction were also common. Six studies (238 allografts) did not report complications. Therefore there were 154 complications in 1134 allografts at a mean of 4.7 years across included studies (13.6% complication rate).

3.3.8 Radiological findings

Only a limited number of studies reported radiographic progression of OA at follow up. One study reported no change in Kellgren and Lawrence OA grade in twenty-eight out of thirty-six knees on plain radiographs at a mean follow time of 2.6 years. One study reported no joint space narrowing, whilst other studies reported small reductions in joint space at final follow up. Two studies compared the joint spaces of the same compartment in the contralateral knee and found no statistically significant changes at baseline and final follow up in either compartment. Verdonk et al. reported no degeneration of femoral cartilage in forty-seven per cent and no degeneration in tibial cartilage in forty-one per cent of knees on MRI evaluation at an average of twelve years follow up.

MRI was commonly used to report meniscal extrusion at follow up. Major meniscal extrusion was most commonly defined as more than three millimetres extrusion on a
mid-coronal image. All studies reporting extrusion found evidence of significant extrusion, with most studies reporting either a mean extrusion of more than three millimetres or the majority of allografts classified as ‘extruded’ or ‘major’ extrusion\(^3, 116, 124, 143, 156, 158, 178\).

### 3.3.9 Graft healing

Ha et al. performed second look arthroscopy at an average of 26.3 months for various reasons\(^116\). They found that eleven allografts had completely healed to the capsule, whilst seven had partially detached; there were no cases of complete detachment. Rath et al. found that all ten allografts undergoing post-operative arthroscopy had completely healed to the capsule, and Wirth et al. found that seventeen of nineteen allografts had completely healed at post-operative arthroscopy\(^222, 287\).

Hardy et al. performed MRIs on fourteen of twenty-one patients at six months post-operatively finding fifty-seven per cent total healing, fourteen per cent partial healing and 29 per cent no healing according to the Henning criteria\(^124\). Noyes et al. devised a new score for graft healing using MRI and arthroscopy, reporting a forty per cent complete or partial healing rate\(^205\).

### 3.3.10 Risk of bias

- **Missing studies**

There were no completed registered trials on any searched registry. Only studies written in the English language were reviewed, therefore some otherwise eligible studies may not have been included.
• **Study type**

All studies included in this systematic review were case series. Some studies described control groups, but the selection for each intervention was for specific reasons, such as a change of technique part way through the study\(^3\). Therefore there is a high risk of selection bias in all included studies. A large number of studies were retrospective, which increases the risk of measurement error (Table 3-2).

• **Missing outcomes**

A number of studies did not report failures or complications. These were not included in the analysis of average complication and failure rate. A number of studies specifically excluded patients that had a ‘failed’ treatment from the analysis of PROMs\(^{68,102,238}\). It is likely that patients with failed treatments would have worse PROMs. Moreover, complications or failures were commonly not defined. It is therefore unknown whether some studies did not consider some patients to have had a complication or failure when others did.

### 3.4 Discussion

This systematic review shows that there are significant improvements in all mean PROMs at final follow up. Given the average age at the time of surgery of 33.6 years, baseline PROMs are very low, indicating the severity of the disease burden in patients undergoing meniscal allograft transplantation. It is also important to note that although there are significant gains in PROMs at final follow up, mean scores are still well below top scores in this young patient group. This may reflect either
non-modifiable damage to the knee or the failure of treatment to completely reverse symptoms.

Indications for meniscal allograft transplantation varied amongst studies, but all studies required patients to have a symptomatic meniscal deficient compartment of the knee. Therefore it is reasonable that the success or failure of the treatment may be judged against symptom relief, as judged by PROMs. This systematic review has reported a consistent improvement in PROMs in the included studies. These results are roughly comparable to older systematic review results, despite there being many new studies reported\textsuperscript{76, 91, 126}. This is the strongest evidence to date for the effectiveness of meniscal allograft transplantation in patients with a symptomatic meniscal deficient knee. The lack of RCTs means that inferences cannot be drawn with confidence, but the results do show that there is a reasonable chance that meniscal allograft transplantation is effective. This is an important MRC framework guidance objective to achieve before a pilot trial is undertaken\textsuperscript{75}.

One trend change in newer studies has been the more common usage of fresh frozen allografts over other preservative methods. Cryopreservation involves controlled freezing to around -196 degrees Celsius with the meniscus bathed in cryoprotectant and then thawed under strict protocols. There is no strong evidence that cryopreservation maintains the integrity of the meniscal allograft better than standard freezing\textsuperscript{185}. Cryopreservation also requires strict thawing protocols, which are difficult to achieve in the clinical environment. These factors may have contributed to the increased use of fresh frozen allografts.
Performing meniscal allograft transplantation on patients with severe OA (radiographic or at arthroscopy) appears controversial, with the majority of studies excluding these patients. It is widely thought that these patients would have worse clinical outcomes and a high failure rate due to the adverse biomechanical environment in the knee\textsuperscript{276}. However, this systematic review has shown that some studies did not exclude these patients, reporting reasonable results. Current practice at UHCW is to include patients with advanced cartilage damage. In chapter six a survival analysis was undertaken to determine whether severe cartilage damage is a predictor of failure.

Another controversy is the method of meniscal root fixation. This systematic review shows that bone plug or bone bridge fixation remains the most popular method, although an all suture technique through bone tunnels is used in significant numbers. There is also a USA – Europe divide, with USA surgeons favouring bone techniques and European surgeons favouring soft tissue fixation. Abat et al. reported more cases of major meniscal extrusion on MRI in patients that had suture fixation of grafts when compared to bone plug fixation\textsuperscript{3}. However conclusions from this should be drawn with caution as the two groups were not directly comparable and should thus the study should be considered as a parallel case series. Bone fixation is often done in the hope that it provides a stronger fixation, whilst an all suture technique is less technically demanding. A biomechanical study has shown a similar pull-out strength with either technique\textsuperscript{133}, whereas another showed that a suture only technique allows a slightly higher contact pressure on the tibial cartilage\textsuperscript{186}.

In general the quality of evidence was low, with the vast majority of studies being case series. Due to the low quality of studies, there is a high risk of biased results.
Patients that were described as having a failed treatment were often excluded from analysis which could lead to an over estimation of the benefit of treatment. The wide variation in failures and complications also suggests that some reporting was more detailed than others. Therefore failures and complications may also be underreported.

3.5 Conclusion

This systematic review shows a consistent improvement in all used PROMs for meniscal allograft transplantation at final follow up. The quality of included studies was low and there were no RCTs. However, the results of this systematic review confirm that there is a reasonable chance that meniscal allograft transplantation improves PROMs in patients with a symptomatic meniscal deficient knee. The majority of studies excluded patients with severe radiographic OA (or advance cartilage damage on arthroscopy) due to the perceived increased risk of failure. This systematic review does not provide evidence to support the hypothesis that meniscal allograft transplantation is chondroprotective. This was addressed in chapter four of this thesis.
4 Is Meniscal Allograft Transplantation Chondroprotective? A Systematic Review of Radiological Outcomes

Declarations

The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Ben Parkinson.

This chapter has been published:


This chapter has been presented:


British Association for Surgery of the Knee, Telford UK, 2015. Can Meniscal Allograft Transplantation Reduce Osteoarthritis Progression? (Eposter)

Funding body

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4.1 Introduction

Chapter two demonstrated it is scientifically plausible that meniscal allograft transplantation might be chondroprotective. This is supported by animal studies\textsuperscript{150, 256}, but has yet to be adequately examined in humans\textsuperscript{126}. Published systematic reviews have focussed on symptomatic relief and functional improvement following meniscal allograft transplantation\textsuperscript{76, 91, 126, 167}. The systematic review in chapter three has also shown that clinical scores were consistently improved following meniscal allograft transplantation. Whilst longer term improvement (or lack of decline) in functional scores may be supportive of the hypothesis that meniscal allograft transplantation is effective, direct evidence that it is chondroprotective is needed. Therefore, the primary objective was to systematically review studies that have reported changes in radiological measures of OA progression following meniscal allograft transplantation.

The scientific plausibility of the hypothesis that meniscal allograft transplantation is chondroprotective relies on the transplant functioning in a similar way to the native meniscus. Cadaveric studies have shown that it was able to perform the primary function of the native meniscus in a similar way by distributing load. The ability to perform this function in patients relies on the transplant maintaining its integrity within the knee over time. This cannot be replicated in cadaveric studies and must be assessed in patients following meniscal allograft transplantation. Therefore, the secondary objective was to systematically evaluate studies that had reported radiological measures of meniscal integrity following meniscal transplantation.
4.2 Materials and Methods

4.2.1 Quality of methodology

This study has been reported in accordance with the PRISMA statement for reporting systematic reviews\textsuperscript{173}. The protocol was published on PROSPERO, the York prospective register of systematic reviews prior to undertaking the searches. A copy of the published protocol can be found in Appendix B.

4.2.2 Eligibility criteria

Study type

• Any clinical study (RCT, non-randomised comparative study or case series) written in the English language. Studies that do not contain new patient data, biomechanical studies and case reports were excluded

Participants

• Any human of any age

Intervention

• Meniscal allograft transplantation using any allograft preserving method and any grafting technique

• Any rehabilitation regime post-operatively

Comparator

• If a comparator group existed, it had to be a reasonable alternative treatment, for example a non-operative rehabilitation group. It was also considered reasonable to use the participants’ other knees as a comparator
Outcome measures

- The primary outcome measure was change in any radiological OA progression measure at a minimum of one year post-intervention
- The secondary outcome measures included MRI measures of the meniscus at a minimum of six months post-intervention, including: Meniscal appearance, signal intensity, healing and extrusion

4.2.3 Search strategy

The search strategy was sensitivity maximising in order to reduce the risk of failing to identify eligible studies. The published search strategy was developed using a combination of keywords and subject headings, which were exploded to maximise the inclusion of potentially relevant studies. The search strategy for Medline (Ovid) (Table 4-1) was adapted for Embase (Ovid) and CENTRAL. The references of all included studies were searched for further potentially relevant studies.

Table 4-1: Ovid Medline search (1946 to May week 4, 2014), Performed on 9th June 2014

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Menisci, Tibial/</td>
<td>6117</td>
</tr>
<tr>
<td>2</td>
<td>Menisc*.mp.</td>
<td>11153</td>
</tr>
<tr>
<td>3</td>
<td>(allograft* or transplant*).mp.</td>
<td>526495</td>
</tr>
<tr>
<td>4</td>
<td>1 or 2</td>
<td>11153</td>
</tr>
<tr>
<td>5</td>
<td>3 and 4</td>
<td>808</td>
</tr>
<tr>
<td>6</td>
<td>(case series or compar* or randomi* or clinical or trial*).mp.</td>
<td>6223122</td>
</tr>
<tr>
<td>7</td>
<td>5 and 6</td>
<td>473</td>
</tr>
<tr>
<td>8</td>
<td>limit 7 to (English language and humans)</td>
<td>342</td>
</tr>
</tbody>
</table>
4.2.4 Selection and appraisal method

Figure 4-1 shows a flow diagram of the selection process. Results of the database searches were transferred into EndNote reference manager and duplicates were discarded. Eligibility criteria were used to assess the remaining studies from the title and abstract. The full papers of any remaining studies were then reviewed. Two reviewers (NS and BP) independently assessed studies for eligibility. Any discrepancies were resolved by discussion and if that failed, by the judgement of TS.

![Flow diagram of the study selection process](image)

In order to reduce duplicate publication bias, if two or more eligible studies used some or all of the same participants, both studies were only included if different outcome measures were used. If multiple studies with the same patient cohort were included on this basis, duplicated outcome measures were only be reported from the study with the longest follow up.
4.3 Results

There were 1056 meniscal allograft transplantations included across thirty-eight studies that met the eligibility criteria (Table 4-2 and Table 4-3). A number of studies included some or all of the same patients as other included studies, but analysed different outcome measures. There were no RCTs, with the majority of studies being case series. Two studies used the contralateral knee as a comparator group. The indications for meniscal allograft transplantation in all studies were a symptomatic knee with a history of meniscectomy. Most patients were young, with nearly all patients being between fifteen and fifty years of age. The most common graft preservation technique was fresh frozen, although some studies used cryopreserved and some older studies used irradiation as well. Bone tunnels or bridges were the most common method of fixing the graft but a number of studies used an all suture technique.

4.3.1 Osteoarthritis progression measures

- Joint space width

Sixteen studies with a total of 428 knees reported the change in joint space width between baseline and final follow up (Table 4-2). The semi-flexed weightbearing position was usually used for joint space width measurement, with Ha et al. also measuring joint space width in full extension. The weighted mean joint space narrowing across all studies was 0.032 millimetres at a mean follow up of 4.5 years (Figure 4-2). Sekiya et al. used the contralateral knee for comparison of joint space width change, finding no significant differences and very similar mean joint space
width changes between the operative and contralateral (comparator) knees\textsuperscript{241}. Rath et al. also used the same compartment in the contralateral knee, finding no significant differences, although there were only eleven patients\textsuperscript{222}. Two studies looked for a correlation between meniscal extrusion and joint space narrowing, with Ha et al. finding a statistically significant intermediate correlation but Lee et al. finding no correlation\textsuperscript{116, 168}. A number of studies found an increase in joint space width, but none were statistically significant\textsuperscript{4, 116, 154, 155}. The majority of studies found a trend towards joint space narrowing, but only two studies reported a statistically significant joint space narrowing\textsuperscript{131, 168}.

Figure 4-2: Forest plot of joint space width loss in each study and a weighted mean using all studies. The X-axis denotes joint space width loss; therefore a negative number constitutes a joint space gain. Lateral meniscal allograft transplantation group (L), medial meniscal allograft transplantation group (M), bone fixation group (B), suture fixation group (S).
The Kellgren and Lawrence (KL) classification is graded from 0 to 4, with grades 1 and 2 depending on the size of the osteophyte, grade 3 depending on a moderate joint space narrowing and grade 4 needing additional subchondral sclerosis. Three studies reported KL scores (Table 4-2). Vunderlinckx et al. had the longest mean follow up of 8.8 years, finding no change in nineteen of thirty-three patients. The other two studies had a much shorter follow up, with Ha et al. reporting no change in twenty-eight patients and one grade worsening in eight patients at a mean 2.6 years; Chalmers et al. reported five patients with no change and five with progression at a mean of 3.3 years.

The Fairbank’s radiological signs include spurring of the tibial spines, marginal osteophytes, flattening of the femur/tibia and joint space narrowing. Three studies reported Fairbank’s classification, with varying outcomes (Table 4-2). Wirth et al. reported that twenty-one of twenty-three patients had less than two signs at baseline. Eleven patients reached final follow up of fourteen years, all of which had progression to two or more signs. It was noted that seventeen of twenty-three patients had irradiated lyophilised grafts and only these patients had arthritic changes. Hommen et al. reported a mean pre-operative score of 0.5 and a mean score of 1.3 at follow up of 11.8 years (p=0.0001). They also reported a tendency for lower Lysholm scores if the Fairbank score had worsened, although this was not statistically significant. The study by van Arkel et al. found no change in eighteen
and an improvement in five patients, although the study had a shorter follow up of three years\textsuperscript{265}.

- \textit{IKDC radiological scores}\textsuperscript{139}

The IKDC radiological score was first presented in 1991, then modified in 2000 and is scored as: no changes, mild, moderate or severe - depending on the severity of a number of radiological markers (joint space narrowing, osteophytes and subchondral sclerosis)\textsuperscript{69, 139}. Two studies used this classification, with Sekiya et al. finding minimal changes at a mean of 2.8 years and Graf et al. finding one grade worsening in one of eight patients at a mean of 8.5 years\textsuperscript{111, 241}.

- \textit{Articular Cartilage Changes on MRI}

Three papers had reported a modified Yulish score to grade articular cartilage degeneration on MRI (Table 4-3)\textsuperscript{294}. The modified Yulish score consists of four grades, which correlate to the Outerbridge arthroscopic grading system of chondral lesions\textsuperscript{211, 274}. Ha et al. noted an absence of further articular cartilage degeneration in seventy-eight per cent of patients at 2.6 years, with the remaining twenty-two per cent progressing by one or two grades\textsuperscript{116}. Marcacci et al. reported a significant improvement in the mean articular cartilage degeneration by half a grade on both the femoral and tibial articular surfaces\textsuperscript{178}. Verdonk et al. reported the longer term articular cartilage changes on seventeen patients over an average of twelve years\textsuperscript{274}. There was no further progression of articular cartilage degeneration on the femoral condyle and tibial plateau in forty-seven per cent and forty-one per cent of patients.
respectively, including thirty-five per cent of patients with no progression on both sides of the joint.

- Other measures

One study reported OA progression at two and ten year follow up with an indeterminate tool\(^5^9\). At two years there was no change in thirty-two of thirty-four patients, but by ten years nearly half of the patients had a mild change and five had moderate or severe progression of OA.

Table 4-2: Studies with radiological OA progression measures. Bone fixation group (B), suture fixation group (S)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (allografts)</th>
<th>Follow up mean – years (range)</th>
<th>Number of allografts with x-ray follow up</th>
<th>Joint space width - mm pre-op (follow up)</th>
<th>Other OA progression measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abat et al. (2013)</td>
<td>88 (88)</td>
<td>5 (2.5-10)</td>
<td>88</td>
<td>S – 3.2 (3.2) B – 3.1 (3.5)</td>
<td>OA progression, number of patients: 2 yrs: 32 no change, 2 mild 10 yrs: 14 no change, 15 mild, 5 moderate/severe</td>
</tr>
<tr>
<td>Carter et al. (2012)</td>
<td>40 (41)</td>
<td>10. X-ray follow up 2 and 10 years</td>
<td>34</td>
<td></td>
<td>KL change: 5 - no change 5 - 1 or more grade change</td>
</tr>
<tr>
<td>Chalmers et al. (2013)</td>
<td>13 (13)</td>
<td>3.3 (1.9-5.7)</td>
<td>10</td>
<td></td>
<td>IKDC radiographic scores: Pre op – 1 normal, 5 abnormal, 2 severely abnormal. Follow up – 1 normal, 4 abnormal, 3 severely abnormal</td>
</tr>
<tr>
<td>Graf et al. (2004)</td>
<td>8 (8)</td>
<td>9.7 (8.5-10.3)</td>
<td>8</td>
<td>Mean loss medial: 0.38 (range -2.75 – 1.75) Lateral: 0.5mm (range 0 – 1.75mm)</td>
<td>KL change: 28 – no change 8 – 1 grade worse Modified Yulish: 78% no change 22% 1 or 2 grades worse</td>
</tr>
<tr>
<td>Ha et al. (2010)</td>
<td>36 (36)</td>
<td>2.6 (2 – 3)</td>
<td>36</td>
<td>Extension: 5.07 (5.0) Rosenberg: 4.14 (4.27)</td>
<td>KL change: 12 of 15 patients had a worsening Fairbank</td>
</tr>
<tr>
<td>Hommen et al. (2007)</td>
<td>20 (20)</td>
<td>11.8 (9.6 – 13.9)</td>
<td>15</td>
<td>5.15 (4)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Score Pre</td>
<td>Score Post</td>
<td>Score Post</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Kim et al. (2011)</td>
<td>27 (29)</td>
<td>4.5 (2 – 10.3)</td>
<td>3.6 (3.7)</td>
<td></td>
<td>Mean scores: 0.5 pre op and 1.3 post op</td>
</tr>
<tr>
<td>Lee et al. (2010)</td>
<td>43 (43)</td>
<td>5.1 (3.5 – 8.3)</td>
<td>43</td>
<td></td>
<td>All: 3.65 (3.35) Extruded: 4.14 (3.87) Non-extruded: 3.3 (3.01)</td>
</tr>
<tr>
<td>Marcacci et al. (2012)</td>
<td>32 (32)</td>
<td>3.4 (3 – 5.5)</td>
<td>32 (MRI)</td>
<td></td>
<td>Modified Yulish (median): Femoral pre op 1.5, follow up 1 Tibial pre op 1, follow up 0.5</td>
</tr>
<tr>
<td>Noyes et al. (2004)</td>
<td>38 (40)</td>
<td>3.3 (2 – 5.7)</td>
<td>40</td>
<td></td>
<td>3 knees showed joint space loss</td>
</tr>
<tr>
<td>Rath et al. (2001)</td>
<td>18 (22)</td>
<td>5.4 (2 – 8)</td>
<td>11</td>
<td>5.2 (4.5). 1 patient lost more than 1mm</td>
<td></td>
</tr>
<tr>
<td>Ryu et al. (2002)</td>
<td>25 (26)</td>
<td>2.8 (1 – 6)</td>
<td>8 (min 2 years fu)</td>
<td>5 - no change 2 – 1-2mm loss 1 – &gt;2mm loss</td>
<td></td>
</tr>
<tr>
<td>Saltzman et al. (2012)</td>
<td>22 (22)</td>
<td>8.5 (6.8 – 11.2)</td>
<td>6 (mean 8.8 years fu)</td>
<td>2 – no loss 2 – minor loss 1 – mild/mod loss 1 – loss</td>
<td></td>
</tr>
<tr>
<td>Sekiya et al. (2003)</td>
<td>28 (28)</td>
<td>2.8 (1.8 – 5.6)</td>
<td>26</td>
<td>Mean loss Medial: Transplant 0.05 Control 0.1 Lateral: Transplant +0.6 Control +0.4</td>
<td>IKDC radiographic scores: Pre op: 6 normal, 13 nearly normal, 7 abnormal, 3 severely abnormal Post op: 4 normal, 12 nearly normal, 10 abnormal, 2 severely abnormal</td>
</tr>
<tr>
<td>Stollsteimer et al. (2000)</td>
<td>22 (23)</td>
<td>3.3 (1.1 – 5.8)</td>
<td>23</td>
<td>Mean loss 0.88 (range 0-3)</td>
<td></td>
</tr>
<tr>
<td>van Arkel et al. (1995)</td>
<td>23 (23)</td>
<td>3 (2 – 5)</td>
<td>23</td>
<td>Fairbank’s criteria: 18 – no change 5 - improvement</td>
<td></td>
</tr>
<tr>
<td>Verdonk et al. (2006)</td>
<td>38 (39)</td>
<td>12.1 (10 – 14.8)</td>
<td>25 (mean 12 year fu)</td>
<td>13 – no loss 12 – unspecified loss</td>
<td>Modified Yulish: No change femoral side in 47%. No change on tibial plateau in 41%</td>
</tr>
<tr>
<td>Vunderlinck et al. (2010)</td>
<td>34 (35)</td>
<td>8.8 (5.2 – 14.1)</td>
<td>33</td>
<td>KL grade: 19 – no change 8 – 1 grade worse 6 – 2 grades worse</td>
<td></td>
</tr>
</tbody>
</table>
| Wirth et al. (2002)    | 23 (23)  | 14 (14) | 23         | Fairbank’s criteria: Pre op: 8 no changes, 13 grade 1, 1 grade 2.
4.3.2 Magnetic resonance imaging measures

Twenty-six of the thirty-eight studies included in this systematic review reported MRI findings following meniscal allograft transplantation.

- **Meniscal extrusion**

Eighteen of the twenty-six studies with MRI outcomes reported meniscal extrusion, with variable techniques (Table 4-3). The methods used to report meniscal extrusion included the absolute number of millimetres the graft extended beyond the edge of the tibial plateau, the relative percentage extrusion of the meniscus that extended beyond the edge of the tibial plateau, as well as a variety of classification systems. The most commonly reported classification defined extrusion as: No extrusion, minor extrusion (less than three millimetres) and major extrusion (more than three millimetres), in relation to the margin of the tibial plateau.², ³, ⁷, ²¹, ²⁷, ²⁸, ³⁰, ³⁴, ³⁶, ³⁷, ³⁸.

All studies reported there was extrusion in the majority of patients, with eleven studies reporting an average extrusion of between 1.7 mm and 5.8 mm.²⁴, ⁷⁹, ¹²⁴, ¹⁴³, ¹⁵⁶, ¹⁵⁸, ¹⁶⁹, ²⁰⁷, ²⁷², ²⁹². Eight studies quantified extrusion by the relative percentage extrusion of the meniscal allograft and reported a mean range from 19.4 to 56.7%.², ³⁹, ¹²⁴, ¹⁴³, ¹⁵⁶, ¹⁵⁸, ¹⁶⁹, ²⁹². Six studies (eight groups) compared the amount of extrusion...
between medial and lateral meniscal allografts, with three finding no difference\textsuperscript{3, 143}, three finding more lateral extrusion\textsuperscript{79, 158, 178} and two finding more medial extrusion\textsuperscript{79, 292}.

The correlation between meniscal extrusion and clinical outcomes had been analysed by ten studies, with seven finding no significant association\textsuperscript{3, 124, 143, 158, 168, 178, 273}. Potter et al. reported poorer clinical outcomes in eleven patients with meniscal extrusion, although these patients represented a subset that all had moderate to severe articular cartilage degeneration at the time of transplantation\textsuperscript{219}. Yoon et al. and Lee et al. found an association between meniscal extrusion and Lysholm score but no did not discuss the finding any further\textsuperscript{168, 292}.

Four papers investigated the effect of surgical technique on the amount of meniscal extrusion. Abat et al. reported a relative percentage extrusion of 36.3\% with root fixation using sutures through bone tunnels, compared to 28.1\% with root fixation using bone plug fixation\textsuperscript{4}. There was no association found between the degree of extrusion and functional scores. Choi et al. evaluated the position of the bone bridge in lateral meniscal transplants, finding an association with meniscal extrusion and increased lateral positioning of the bone bridge\textsuperscript{64}. Jang et al. compared the traditional Pollard sizing technique to Pollard minus five per cent sizing\textsuperscript{143}. The relative percentage extrusion decreased from 46.7\% to 35.2\%, but no difference in clinical or other radiographic outcomes was found. De Coninck et al. compared open to arthroscopic surgical technique for meniscal allograft transplantation\textsuperscript{79}. In the open technique, the meniscal roots were sutured to the capsule and native meniscal remnants, while in the arthroscopic technique the meniscal roots were secured by
suture fixation through bone tunnels. They found significantly less meniscal extrusion with the arthroscopic technique.

Three papers evaluated the change in meniscal extrusion over time. Lee et al. evaluated meniscal extrusion over the first year post-operatively by serial MRI scans (six weeks, three, six and twelve months), finding that average meniscal extrusion didn’t differ at any time point\textsuperscript{169}. Hardy et al. reported 2.7 mm meniscal extrusion at six months post-operatively and 3.6 mm at final follow up of 4.4 years\textsuperscript{124}. The series consisted of twenty-two patients and it was not stated if the MRI scans at final follow up were from the same patients as the six month MRI scans. Verdonk et al. evaluated the long term change in meniscal extrusion from one year to an average of twelve years, finding progressive meniscal extrusion in fifty-nine per cent of cases\textsuperscript{274}. However extrusion had no correlation with progressive articular cartilage degeneration or any of the clinical outcome measures.

All except two studies evaluated meniscal extrusion with knees in a non-weight bearing position. Noyes et al. performed MRI scans on twenty-nine meniscal allografts under weight bearing conditions and demonstrated a mean of 2.2 mm extrusion\textsuperscript{206}. Verdonk et al. evaluated the effect of weight bearing on meniscal extrusion with the use of ultrasound\textsuperscript{272}. Ten transplanted lateral meniscal allografts and ten healthy lateral menisci were studied in the supine non-weight bearing position, bipedal stance and unipedal stance. Mean extrusion was higher in all positions for the transplanted menisci compared to normal menisci. The mean extrusion however did not increase during weight bearing conditions in either group.

- Signal intensity
Ten studies reported on the signal intensity characteristics of meniscal allografts, with all but one study reporting altered and increased signal changes in the majority of the meniscal allografts (Table 4-3). Lee et al. evaluated the intra-meniscal signal intensity of forty-three meniscal allografts with serial MRI scans over the first year (six weeks, three, six and twelve months)\textsuperscript{170}. They standardised the signal intensity within the meniscal allograft to the normal ipsilateral meniscus. The intra-meniscal signal intensity was higher within all the allograft menisci at all time points, with a significantly increased signal starting at three and six months for the anterior and posterior horns respectively. They found no correlation between intra-meniscal signal intensity and clinical outcomes. Hardy et al. also reported on the meniscal allograft appearance at six months and 4.4 years\textsuperscript{124}. At six months they found eighty-six per cent of menisci returned a normal homogenous appearance, compared to only 26% at 4.4 years. Verdonk et al. found the majority of meniscal allografts had increased signal intensity at twelve years, with eighty-two per cent having no progression of their signal intensity from one year to final follow up\textsuperscript{274}.

- **Meniscal size and shape**

Ten studies reported size and shape changes of meniscal allografts after transplantation (Table 4-3). Meniscal shrinkage was reported by multiple studies, with Carter et al. demonstrating an average of seven per cent volume loss over the first six months\textsuperscript{58}. Kim et al. and Zhang et al. found shrinkage to predominantly affect the anterior horn of the meniscus\textsuperscript{156,295}. Zhang et al. also performed a second look arthroscopy, which confirmed atrophy and fraying of the anterior meniscus horn that corresponded to the MRI changes in the same region.
Meniscal healing

MRI assessment of allograft healing to the capsule was reported by six studies (Table 4-3). Three studies reported a healing rate of 100%\textsuperscript{35,168,178}, whilst the others reported some partial and non-healing menisci. The study by van Arkel et al. correlated MRI healing to arthroscopic healing at a mean of three years post operatively on nineteen patients. They found complete healing in sixty-three per cent, partial healing in twenty-six per cent and no healing in eleven per cent of cases on MRI scans. However, MRI was found to underestimate healing rates; the cases with partial healing on MRI were found to be completely healed at arthroscopy and the cases with no healing on MRI were found to be partially healed at arthroscopy.

Table 4-3: Studies with MRI measures of meniscal integrity. Full weight bearing (FWB), partial weight bearing (PWB), week (w), month (m), suture fixation group (S), bone fixation group (B), medial meniscus group (MM), lateral meniscus group (LM) Relative percentage extrusion (RPE).

<table>
<thead>
<tr>
<th>Study</th>
<th>No. patients (knees)</th>
<th>Follow up mean – years (range)</th>
<th>No. MRI</th>
<th>MRI Signal Intensity</th>
<th>MRI extrusion Minor &lt;3mm Major &gt;3mm</th>
<th>MRI – size and shape</th>
<th>MRI – allograft healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abat et al. (2012)</td>
<td>88 (88)</td>
<td>Min 3 yrs</td>
<td>88</td>
<td></td>
<td>S: RPE 36.3% Minor 27% Major 73% B: RPE 28.1% Minor 69% Major 31%</td>
<td></td>
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<tr>
<td>Bhosdale et al. (2007)</td>
<td>8 (8)</td>
<td>3.2 (2-6)</td>
<td>5</td>
<td>Increased internal 100%</td>
<td>Wedge 100% Flattened 40% Expanded 20% Irregular surface margin 80%</td>
<td></td>
<td>Healed 100%</td>
</tr>
<tr>
<td>Carter (2013)</td>
<td>25 (25)</td>
<td>0.5</td>
<td>25</td>
<td></td>
<td>Shrinkage avg 7% (0-22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>N (n)</td>
<td>Mean (Range)</td>
<td>Outcome</td>
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<td></td>
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<tr>
<td>Choi et al. (2011)</td>
<td>23 (23)</td>
<td>0.5</td>
<td>23</td>
<td>Mean 3.2mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha et al. (2010)</td>
<td>36 (36)</td>
<td>2.6 (2–3)</td>
<td>36</td>
<td>Complete 72% Partial 28%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardy et al. (2013)</td>
<td>22 (22)</td>
<td>4.4 (2.8–6)</td>
<td>14 at 6m 17 at final</td>
<td>6m – Complete healing 57% Partial healing 14% Not healed 29%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hommen et al. (2007)</td>
<td>20 (20) + 2 without scores</td>
<td>11.8 (9.6–13.9)</td>
<td>7</td>
<td>Grade 3 71%</td>
<td>All moderate shrinkage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jang et al. (2011)</td>
<td>36 (36)</td>
<td>2.6 (2-3)</td>
<td>36</td>
<td>Traditional Pollard: Mean 4.1mm RPE 46.7% None 6% Minor 11% Major 83% Modified Pollard: Mean 3.7mm RPE 35.2% None 6% Minor 28% Major 66%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td>106 (110)</td>
<td>4.1 (2–13.6)</td>
<td>108</td>
<td>Normal 7% Variable 93%</td>
<td>Normal volume 69% Atrophy 3% Atrophy anterior horn 19% Atrophy posterior horn 4% Swollen anterior horn 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2012)</td>
<td>31 (31)</td>
<td>1</td>
<td>31</td>
<td>Shrinkage: Minimal 65% Mild 19% Moderate 16% Severe 0% Width midbody 89% Thickness midbody 115%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al.</td>
<td>43 (43)</td>
<td>1</td>
<td>43</td>
<td>Higher</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95
<table>
<thead>
<tr>
<th>Study</th>
<th>n (N)</th>
<th>signal intensity</th>
<th>% healed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (2010)</td>
<td>43 (43)</td>
<td>5.1 (3.5 – 8.3)</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 3.0mm</td>
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<tr>
<td></td>
<td></td>
<td>Minor 60%</td>
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<tr>
<td></td>
<td></td>
<td>Major 40%</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2008)</td>
<td>21 (21)</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6w: Mean 2.9mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 29.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3m: Mean 2.9mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 29.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6m: Mean 3.0mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 32.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12m: Mean 2.9mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 31.9%</td>
<td></td>
</tr>
<tr>
<td>Koh et al. (2012)</td>
<td>99 (99)</td>
<td>2.7 (2 – 4.9)</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LM: Mean 4.7mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 52%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MM: Mean 2.9mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE 31.2%</td>
<td></td>
</tr>
<tr>
<td>Marcacci et al. (2012)</td>
<td>32 (32)</td>
<td>3.4 (3 – 5.5)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of grafts with extrusion 69% overall MM 50% LM 87%</td>
<td>Healed 100%</td>
</tr>
<tr>
<td>Noyes et al. (2004)</td>
<td>38 (40)</td>
<td>3.3 (2 – 5.7)</td>
<td>29 FWB or PWB conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal 3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 1 45%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 2 38%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 2.2mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;25% meniscal width 59%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 – 50% meniscal width 38%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50% meniscal width 3%</td>
<td></td>
</tr>
<tr>
<td>Potter et al. (1996)</td>
<td>24 (29)</td>
<td>1 (0.25 – 3.4)</td>
<td>29 FWB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased periphera l signal 100%. Increased signal posterior horn attachment site 63%</td>
<td>Moderate 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe 14%</td>
<td></td>
</tr>
<tr>
<td>Rankin et al. (2006)</td>
<td>8 (8)</td>
<td>2 (1.3 – 2.8)</td>
<td>8 FWB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean height and width similar to normal meniscus</td>
<td></td>
</tr>
<tr>
<td>Stollsteimer et al. (2000)</td>
<td>22 (23)</td>
<td>3.3 (1.1 – 5.8)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased signal 42%</td>
<td>No extrusion 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor 8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume shrinkage to 62% of normal</td>
<td></td>
</tr>
<tr>
<td>van Arkel et</td>
<td>16 (19)</td>
<td>2.6 (1.2 – 4.6)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sub extrusion 65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate shrinkage</td>
<td>Complete healing</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Immediate Postoperative</td>
<td>Follow-up</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>-------------------------</td>
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<tr>
<td>al. (2000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verdonk et al. (2004)</td>
<td>17 (17)</td>
<td>2 (0.5 – 9.25)</td>
<td>17</td>
</tr>
<tr>
<td>Verdonk et al. (2006)</td>
<td>38 (39)</td>
<td>12.1 (10 – 14.8)</td>
<td>10yr: 25 1 &amp; 10yr: 17</td>
</tr>
<tr>
<td>De Coninck et al. (2012)</td>
<td>37 (37)</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Wirth et al. (2002)</td>
<td>23 (23)</td>
<td>14 (14)</td>
<td>9</td>
</tr>
<tr>
<td>Yoon et al. (2014)</td>
<td>91 (91)</td>
<td>3.3 (2 – 10.4)</td>
<td>35</td>
</tr>
<tr>
<td>Zhang et al. (2012)</td>
<td>18 (18)</td>
<td>2.1 (1.5 – 3.4)</td>
<td>17</td>
</tr>
</tbody>
</table>
4.3.3 Risk of bias

- **Missing studies**

Only published studies were searched for, which may exacerbate publication bias. Secondly, studies written in languages other than English were not included, which may have resulted in some important studies being lost.

- **Missing outcomes**

Most studies had patients that were lost to follow up. Whilst this is inevitable, especially in studies with long term follow up, it can introduce bias. It was common for studies to exclude failures from follow up assessment. This is highly likely to bias results towards better outcome scores. It was also common for some patients to not have imaging at follow up. It was not always clear why some patients did and others did not have follow up imaging, but this was a potential source of bias.

4.4 Discussion

There has been substantial research interest in assessing whether interventions can modify the long term disease process of OA. Radiological markers for joint damage, especially joint space narrowing, have become widely accepted as appropriate surrogate measures of OA progression and have been recommended as the outcome measure of choice by regulatory agencies in the United States and Europe\(^3\). It has been shown that joint space narrowing is highly predictive of the need for future OA related surgery (usually total knee replacement)\(^4\). Bruyere et al. found that the relative risk for future OA related surgery with a joint space narrowing of 0.7 mm or more over three years was 5.15 (95% confidence interval 1.7 – 15.6)\(^5\). A recent systematic review assessing the imaging options for OA progression concluded that
joint space narrowing was the only imaging tool that should be recommended for the assessment of OA progression in clinical trials. Given that patients with a symptomatic meniscal deficient knee have a high rate of knee OA progression, the negligible (0.032 mm) joint space narrowing at 4.5 years in patients following meniscal allograft transplantation provides some support for the hypothesis that it may be chondroprotective. As well as this, the two studies that used the contralateral normal knee as a comparator of joint space changes found no significant differences between the groups at final follow up.

It is possible that joint space width on plain radiography is not an accurate measure of cartilage loss in patients undergoing meniscal allograft transplantation because joint space width is affected by meniscal volume and position. Other limitations of plain radiography is that it is insensitive to early changes or focal disease, and joint space width can be affected by changes in the other compartment. The NICE OA guidelines state that valid structural measures of OA progression include MRI features of OA, as well as joint space width. High resolution MRI is increasingly being used as a surrogate endpoint for OA in studies as it is has been shown to be more sensitive and precise. Common MRI measures include cartilage volume or thickness change, T2 mapping, bone marrow lesions, measurement of focal cartilage lesions and bone shape change. Recent studies have shown that statistically significant changes in cartilage volume and thickness can be seen at one year on MRI. It has further been shown that higher cartilage losses are predictive of the need for future knee replacement. A recent systematic review on the use of MRI measures concluded that cartilage volume or thickness change was a viable alternative to joint space width and likely to require fewer participants in RCTs, compared to joint space width. Therefore cartilage volume change was thought to
be the most appropriate primary outcome measure in the pilot RCT comparing meniscal allograft transplantation to physiotherapy.

One of the difficulties with measuring joint space width is that it is time consuming and requires expertise in MRI segmentation techniques. There are relatively few groups that have published studies with MRI volume analysis. One such UK based company is IMorphics, who are based in Manchester. They are world leaders in image analysis and have published their measurement error associated with their techniques, which is favourable to other published studies\(^{46, 283}\). There is also a history of previous successful collaborations between IMorphics and Charles Hutchinson, the author’s supervisor. Therefore IMorphics were used in the pilot RCT to perform the MRI image analysis.

The underlying principle of meniscal allograft transplantation is to restore normal meniscal coverage of the tibial plateau so that it can improve contact biomechanics of the knee. Meniscal extrusion is a surrogate marker to assess the extent to which this has been achieved; minimal extrusion implies good tibial plateau coverage, and vice versa. Studies on native menisci have shown that extrusion is associated with accelerated chondral loss and OA\(^{137, 152, 244, 255}\). It has not been established whether extrusion is an appropriate measure in meniscal allograft transplantation. This systematic review found no clear association between extrusion and other adverse outcomes, suggesting that extrusion may not be an appropriate outcome measure. This may be because meniscal sizing is imprecise and it is possible for an oversized meniscal allograft to restore adequate tibial plateau coverage, whilst exhibiting a large amount of extrusion\(^{187}\). It is also possible that an undersized or shrunken graft does not restore plateau coverage, whilst having minimal extrusion. An additional
limitation is that extrusion was measured in the coronal plane at a single point (the midbody position). Noyes et al. and Marcacci et al. demonstrated minimal extrusion in the sagittal plane, suggesting the assumption that extrusion is uniform may be incorrect for meniscal allograft transplantation\textsuperscript{178, 206}. Therefore measuring extrusion at a single point on a single plane may not be an accurate measure of either total extrusion or tibial plateau coverage. High resolution MRI may be able to provide a better measure by 3D modelling the meniscus and tibial plateau.

MRI has become the investigation of choice to assess meniscal allograft integrity and healing, as it is cost effective and non-invasive. This systematic review found high rates of meniscal healing to the capsule, whilst signal intensity and meniscal shape was predominantly altered. Studies have shown that the meniscus is repopulated by cells resembling fibrochondrocytes in the first six months, but the normal meniscal collagen architecture, orientation and histological appearance was changed\textsuperscript{15, 16}. A correlation between MRI and histological appearance has been shown, with biopsies from areas of homogenous low signal demonstrating a near normal collagen appearance and biopsies from areas of high signal showing a disorganised collagen appearance\textsuperscript{219}. Concerns remain over the consequences of this altered tissue structure and the ability of a meniscal allograft to provide chondroprotection, but no association with clinical outcomes has been found\textsuperscript{170, 206, 274}.

\subsection*{4.4.1 Limitations}

The quality of included studies was low, with a high risk of selection and measurement bias. The limited number of studies using control groups also limits the value of results, especially when interpreting OA progression. The studies included
in this systematic review are also heterogeneous, with different inclusion criteria, techniques, graft type, associated procedures, rehabilitation and follow up. This makes a formal meta-analysis inappropriate and limits the strength of conclusions.

### 4.5 Conclusions

Given the lack of high quality controlled trials, it is difficult to draw definitive conclusions. It appears that meniscal allograft transplantation cannot universally reverse or prevent OA changes in patients with a symptomatic meniscal deficient knee. Some studies showed minimal progression of OA in the long term and the mean weighted joint space narrowing was also negligible. These results provide limited for support the hypothesis that meniscal allograft transplantation may be chondroprotective. Given the scientific plausibility that meniscal allograft transplantation may reduce or delay the progression of OA and the limited supporting clinical evidence, a formal evaluation of the intervention is warranted. The first stage of this is developing a pilot trial, which was achieved in chapter seven of this thesis.
5 Physiotherapy for the Treatment of the Meniscal Deficient Knee: A Systematic Review

Declarations

The studies retrieved in the searches were independently reviewed for eligibility by both the candidate and Imran Ahmed.

Funding body

This research was supported by Arthritis Research UK (grant number 20149).

5.1 Introduction

In chapter two it was shown that meniscectomy results in deleterious biomechanical changes in the knee, with a subsequent high risk of developing OA. It was also shown that it is scientifically plausible that physiotherapy could alter the adverse biomechanics, with a potentially delayed or reduced progression of OA in these patients.

Physiotherapy has been shown to be effective in treating patients with symptomatic OA of the knee and is recommended by NICE\textsuperscript{204,263}. It has also been shown to improve function in patients following meniscectomy, in the immediate post-operative period\textsuperscript{80}. However, it has not been established whether a physiotherapy programme can reduce symptoms and OA progression in patients outside of the immediate post-operative period. In order to make a full assessment of
physiotherapy as a comparator in the RCT, the objective of this study was to perform a systematic review of studies that have assessed physiotherapy interventions in patients with a history of meniscectomy, using outcome measures assessing OA risk, progression and/or symptomatic change.

5.2 Methods

This study has been reported in accordance with the PRISMA statement for reporting systematic reviews. A protocol for this systematic review was published before the searches were performed and can be viewed in Appendix C.

5.2.1 Eligibility criteria

Study type

- Any clinical study (RCT, non-randomised comparative study or case series) written in the English language. Studies that did not contain new patient data, for example systematic reviews were excluded, as well as case reports

Participants

- Participants must have had a previous partial or total meniscectomy and be out of the early post-operative period (minimum twelve weeks before being recruited/studied)
- Participants that did not have a previous (partial or total) meniscectomy prior to entering the study were excluded

Intervention
• Any exercise based intervention designed to address the lower limb, delivered or administered by a physiotherapist or equivalent health care practitioner

• No minimum or maximum intervention period

**Comparator**

• A comparator was not a requirement for inclusion but any reasonable comparator was appropriate, including but not limited to, a different exercise intervention, a placebo or further surgery

**Outcome measures**

• Any outcome measures that assessed risk or progression of OA, or any outcome measures that assessed symptoms or function were considered acceptable. Studies were excluded if none of these were reported

5.2.2 Search strategy

The search strategy was developed using a combination of keywords and subject headings, which were exploded to maximise the inclusion of potentially relevant studies. The search strategy for Medline (Ovid) (Table 5-1) was adapted for Embase (Ovid), CENTRAL and the Physiotherapy Evidence Database (PEDro). The references of all included studies were searched for further potentially relevant studies.
Table 5-1: Ovid Medline search, performed on the 26th March 2015

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Physical Therapy Modalities/ or Physical Therapists/</td>
</tr>
<tr>
<td>2</td>
<td>(physical therapy or physiotherapy).mp.</td>
</tr>
<tr>
<td>3</td>
<td>exp Exercise Therapy/ or exercise.mp.</td>
</tr>
<tr>
<td>4</td>
<td>1 or 2 or 3</td>
</tr>
<tr>
<td>5</td>
<td>(meniscectom* or menisectom*).mp.</td>
</tr>
<tr>
<td>6</td>
<td>Menisci, Tibial/ or menisc*.mp.</td>
</tr>
<tr>
<td>7</td>
<td>(loss or deficien* or removal).mp.</td>
</tr>
<tr>
<td>8</td>
<td>6 and 7</td>
</tr>
<tr>
<td>9</td>
<td>5 or 8</td>
</tr>
<tr>
<td>10</td>
<td>4 and 9</td>
</tr>
<tr>
<td>11</td>
<td>limit 10 to (english language and humans)</td>
</tr>
</tbody>
</table>

5.2.3 Selection and appraisal method

Figure 5-1 shows a flow diagram of the selection process. Results of the database searches were transferred into EndNote reference manager and duplicates were discarded. Our eligibility criteria were used to assess the remaining studies using the title and abstract. The full papers of any remaining studies were then reviewed. Two reviewers (NS and IA) independently assessed studies for eligibility. Any discrepancies were resolved by discussion and if that failed, by the judgement of MC.
Figure 5-1: Flow diagram of the study selection process

5.3 Results

The literature search revealed three eligible papers (Table 5-2), although it was determined that the paper by Ericsson et al. was a secondary analysis of the study by Roos and Dahlberg. Both papers were included as they offered different analyses, but it is important to note that the underlying study was the same. Both included studies were RCTs comparing a form of physiotherapy to a control group of no intervention.
Table 5-2: Results of the three eligible papers

<table>
<thead>
<tr>
<th>Study design</th>
<th>Paper</th>
<th>Number in study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Roos and Dahlberg&lt;sup&gt;228&lt;/sup&gt;</td>
<td>166 invited. 81 positive responses. 56 eligible and randomised, 30 completed follow up</td>
<td>Aged 35 – 45 years. History of a medial arthroscopic partial meniscectomy between 3 and 5 years prior to study. Exclusion: ACL rupture, marked visible bone on arthroscopy, physical limitations due to co-morbidities, depression, sick leave or disability pension, lack of walking ability, competitive athletes</td>
<td>Functional exercise training (also called neuromuscular training). One initial session to design a personalised therapy programme then 3 exercise classes a week for 4 months +/- extra unsupervised exercise/sport</td>
<td>A no treatment group</td>
<td>Primary outcome: Change in T1 relaxation time, in the presence of contrast, between baseline and follow up - assessed using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) 15msec versus -15msec (p=0.036). Secondary outcomes: 1 leg jump, square hop, 1 leg running, bicycle ergonometer test</td>
</tr>
<tr>
<td>Secondary analysis of first RCT by Roos and Dahlberg et al.</td>
<td>Ericsson et al.&lt;sup&gt;39&lt;/sup&gt;</td>
<td>166 invited. 81 positive responses. 56 eligible and randomised, 30 completed follow up</td>
<td>Aged 35 – 45 years. History of a medial arthroscopic partial meniscectomy between 1 and 6 years prior to study. Exclusion: ACL rupture (either knee), marked visible bone on arthroscopy, physical limitations due to co-morbid condition, depression, sick leave or disability pension, lack of walking ability, competitive athletes</td>
<td>Functional exercise training (also called neuromuscular training). One initial session to design a personalised therapy programme then 3 exercise classes a week for 4 months +/- extra unsupervised exercise/sport</td>
<td>A no treatment group</td>
<td>Primary outcomes: Between group differences in change from baseline to 4 month follow up – one leg hop distance (p=0.04), square hop (p=0.07), one leg rising (p=0.28). Secondary outcomes: Quads endurance (p=0.001), hamstrings strength (p=0.03), hamstrings endurance (p=0.15), quads strength (p=0.83), KOOS scores (p&gt;0.7)</td>
</tr>
<tr>
<td>RCT</td>
<td>Hall et al.&lt;sup&gt;120&lt;/sup&gt;</td>
<td>415 screened, 259 eligible, 62 randomised, 2 lost to follow up</td>
<td>Aged 30-50 years. History of medial partial meniscectomy between 3 months and 1 year prior to the study. No or mild pain in the knee. Exclusion: Kellgren and Lawrence grade 3-4, other lower limb surgery, ACL or PCL tears, BMI&gt;36, other forms of arthritis, diabetes, cardiac problems limiting activities</td>
<td>12 week neuromuscular exercise programme, with a focus on maintaining neutral alignment and engaging trunk muscles. 8 individual sessions + home sessions</td>
<td>A no treatment group</td>
<td>Primary outcomes: Peak KAM during stance phase of normal walking pace mean difference 0.22 (95% CI -0.11 – 0.55), during sit to stand mean difference -0.01 (95% CI -0.33 – 0.31). Secondary outcomes: Peak KAM through walking and peak knee flexion moment during stance phase, sit to stand, one leg hop, self reported pain and function, KOOS, pain, change in function, muscle strength, physical performance tests</td>
</tr>
</tbody>
</table>
This was a RCT comparing a functional exercise programme to a no intervention group in patients with a history of partial medial meniscectomy (Table 5-2 for details). The authors hypothesised that exercise may prevent structural changes that contribute to the progression of OA following partial meniscectomy. The primary outcome measure was T1 relaxation times using dGEMRIC, which assesses glycosaminoglycan (GAG) content in articular cartilage, which is considered a measure of cartilage quality. The primary outcome measure was a surrogate for OA progression and the authors stated that it was used because more traditional measures, for example plain radiographs are insensitive to early OA changes. Despite a high dropout rate, the authors showed a statistically significant difference between the intervention and a control group at four months (15 msec versus -15 msec p=0.036). They also showed a strong correlation between physical activity level and GAG content in the intervention group, as well as the same finding in the pooled group of all subjects, suggesting a dose-response effect. They concluded that exercise could have a role in OA prevention in high risk patients.

- Assessment of quality

This was a well conducted RCT and reported in line with the CONSORT guidelines\(^{196}\). One important limitation is that there were a large number of post-randomisation withdrawals from the study (twelve in the intervention and fourteen in the control group). This was nearly half of the participants randomised, which appears very high for a short follow up study and risks introducing bias into the
results. This risk was shown to be minimised as the baseline characteristics between the participants lost to follow and those completing the study were similar; the loss to follow up was also similar in both groups. A second limitation was the low external validity; only people with a previous partial medial meniscectomy and a small age range were included, as well as there being a large number of exclusion criteria. The results of this study are therefore less generalisable to the general population of post-meniscectomy patients.

5.3.2 Ericsson et al.98

This was a secondary analysis of the study by Roos and Dahlberg, with different reported outcome measures228. Their hypothesis was that post-meniscectomy patients have functional limitations that may be a risk factor for OA; these functional limitations could be addressed with a functional (neuromuscular) exercise programme. The intervention was described in extensive detail and broadly focussed on the principles of neuromuscular training, but personalised to each participant. This was achieved by a senior physiotherapist having an initial consultation where a diagnosis and treatment plan was devised. The recommended number of treatment sessions was three per week for four months, although the number of sessions attended was often much lower than this (the mean number of sessions attended per participant was thirty-one).

Despite small numbers of participants and a conservative intention-to-treat analysis, the authors reported statistically significant differences in a number of outcome measures and a trend towards significance in a number of others (Table 5-2). They did not show a difference in the KOOS and actual values or confidence intervals were not given. The authors concluded that functional exercise training may have
positive effects on functional performance and thigh muscle strength in this population.

- Assessment of quality

The limitations of this study are as described for the limitations of the study by Roos and Dahlberg with respect to loss to follow up and external validity, as the methodology and participants were the same\textsuperscript{228}. The outcome assessors were also not blinded. It is accepted that it was not possible to blind the participants or person delivering the intervention, but would have been possible to blind the outcome assessor and potentially others, for example the statistician. In fact, the outcome assessors looking at the MRI scans for the original study were blinded\textsuperscript{228}. Therefore, there is a risk of detection bias in this study.

5.3.3 Hall at al.\textsuperscript{120}

This was a RCT comparing a neuromuscular exercise programme to a control group of no intervention (Table 5-2 for details). The primary outcome measure in the trial was knee adduction moment (KAM). KAM is used as an indirect measure of medial tibiofemoral contact force and it is thought that a reduction in this could reduce the risk of OA. It has previously been shown that peak KAM increases following partial meniscectomy and remains high two years post-operatively\textsuperscript{121}. The authors were unable to show a statistically significant difference between the intervention and control group in either of the primary outcome measures (peak KAM in stance phase of normal walking and sit to stand). Of the secondary outcome measures the following were improved in the intervention group compared to control: A perceived
improvement in physical function (relative risk 0.29, 95% CI 0.09 – 0.91) and overall improvement (relative risk 0.38, 95% CI 0.16 – 0.92). Other secondary outcomes showed no statistically significant difference (Table 5-2). The authors concluded that they showed no change in peak KAM and future studies should address the long term effects of neuromuscular exercise on structural measures of OA progression.

- **Assessment of quality**

This was well designed, conducted and reported in accordance with CONSORT guidelines for RCTs\textsuperscript{196}. Of note, the study protocol was published\textsuperscript{119}, a power calculation was performed, a randomised design with adequate allocation concealment was used, intervention fidelity and compliance were monitored and assessors were blinded. The main limitation of the study was the low external validity. Only twenty-four per cent of eligible patients enrolled in the trial and this was after an extensive exclusion list.

5.3.4 **Risk of bias**

- **Missing studies**

Only published studies were searched for, which may exacerbate publication bias. Secondly, only studies written in the English language were included, which may result in some important studies being lost.
• Missing outcomes

The studies of Roos and Dahlberg\textsuperscript{228} and Ericsson et al.\textsuperscript{98} used the same participant group, which had a loss to follow up of twenty-six out of fifty-six. This is high and may have introduced bias. Ericsson et al. used an intention-to-treat analysis, bringing forward baseline results of participants lost to follow up in order to minimise this effect. There was a low loss to follow up in the study by Hall et al.\textsuperscript{120}.

5.4 Discussion

Physiotherapy is a common and widely available intervention to treat musculoskeletal disorders. Its effectiveness in managing patients’ symptoms with established OA is clear,\textsuperscript{263} and it is recommended for use on the NHS by NICE\textsuperscript{204}. Physiotherapy is also used in the post-operative rehabilitation of patients following meniscectomy and a number of RCTs have shown it to be effective in improving patient and assessor reported outcomes\textsuperscript{80}. However, its role in the prevention of the development of OA in patients following meniscectomy is far less clear.

Patients with a history of meniscectomy have a high risk of developing symptomatic OA\textsuperscript{213,229,230}. This systematic review identified only a small number of studies but they were RCTs and were of a medium to high quality. Both studies described adequate randomisation and allocation concealment, therefore reducing the risk of selection bias, and balancing known and unknown confounders.

Roos and Dahlberg showed a statistically significant improvement in GAG content and a strong dose response effect of exercise\textsuperscript{228}. GAG are essential components of
particular cartilage and it is thought that a reduced concentration signifies degradation, leading to OA. Therefore, this study suggests that exercise may have a role preventing the development of OA. dGEMRIC involves MRI scanning after an articular injection of gadolinium. It is being increasingly used to evaluate articular cartilage breakdown and repair. However, the role of dGEMRIC in predicting the development of OA is yet to be definitively established. Despite this, the study did show that the intervention had an effect on articular cartilage compared to controls. This may be suggestive of a chondroprotective effect, although the long term consequences are not known.

Ericsson et al., using the same participants, showed an improvement in some measures of thigh strength and functional performance in the intervention group, compared to the control group. It has previously been suggested that reduced thigh muscle strength and functional performance are predictors of future OA. The same authors, in what appears to be the same participants, showed reduced quadriceps strength in post-meniscectomy patients. Therefore, an intervention that improves thigh strength and functional performance may reduce the risk of OA.

Hall et al. found a difference in perceived improvement in function, but did not find a statistically significant difference in their primary outcome measure of peak KAM. Their conclusion that no difference was found, may have been too strong as despite performing a sample size calculation (power 0.8), it appears that their study may have been underpowered. The mean difference of 0.22 in peak KAM in the stance phase of normal walking exceeded the pre-stated minimum clinically important difference (MCID) of 0.2. Whilst inferences cannot be drawn due to a lack of
statistical significance, a clinically meaningful difference cannot be ruled out. This could only be addressed with a larger study sample.

5.4.1 Limitations

All included papers used surrogate primary outcome measures. A surrogate outcome is not of direct clinical importance but is thought to reflect later clinical outcomes. Surrogate outcomes are commonly used when the clinical outcome is very rare or has a long lag time. They are often quicker, cheaper and require fewer study participants to detect differences\textsuperscript{18}. Detecting disease modification in OA is difficult due to the long lag time from exposure to clearly defined OA. Currently used outcome measures have limitations: Joint space width on plain radiograph (which is in itself a surrogate outcome) is insensitive to early OA changes; joint replacement only reflects end stage OA and is insensitive to early change; a combination of symptoms and radiographic change requires very high participant numbers to detect a moderate difference\textsuperscript{177}. To be useful, a surrogate outcome should be an indication of the pathogenic process or response to a disease modifying intervention. There also needs to be evidence of an association between the surrogate outcome and the clinical outcome of importance. The different surrogate outcome measures used in the included studies have some justification for use and some evidence of associations with clinical outcomes. However, none of the surrogates is considered a gold standard for assessing disease modification in OA and therefore the strength of conclusions must reflect this.

Secondly, both the included studies used a ‘no intervention’ control group in favour of a placebo or alternative treatment. This may mean that some of the improvements seen in the intervention group were as a result of a placebo effect. However, it has
been shown that the placebo effect is negligible for objective outcomes in patients with OA.\textsuperscript{297}

5.5 Conclusion

There is some limited evidence supporting the hypothesis that physiotherapy may be able to reduce the risk of OA in patients with a history of partial meniscectomy. However, the use of surrogate measures with only partially determined utility, a low number of studies and low numbers of participants in the included studies, precludes definitive conclusions from being drawn.

Although there is limited evidence that physiotherapy is chondroprotective in this patient population, there is good evidence that it improves symptoms, function, is safe and is available on the NHS. It was therefore considered to be an appropriate alternative treatment to meniscal allograft transplantation and was used as the comparator for the pilot, in chapter eight.
6 Survival Analysis of a Consecutive Series of Meniscal Allograft Transplantations Performed at UHCW

Declarations

The patient data was prospectively collected by the knee team as part of a service evaluation. The rest of the chapter, including the analyses, were performed by the candidate.

Aspects of this chapter have been presented:

British Association for Surgery of the Knee, Telford UK, 2015. Meniscal Allograft Transplantation: An Analysis of a Consecutive Series of 114 Transplants Based on Pre-operative Articular Cartilage Grade. (Podium)


Funding body

This research was supported by Arthritis Research UK (grant number 20149).

6.1 Introduction

Meniscal allograft transplantation has traditionally been contraindicated in the presence of full thickness articular cartilage loss or severe OA, as it is thought that the biomechanical environment would not be favourable, resulting in a high failure rate. However, it has been reported that up to fifty per cent of patients present with this level of advanced chondral damage. These patients represent a treatment challenge and some studies have looked to extend the indications of meniscal allograft transplantation by performing concomitant chondral repair procedures, with promising clinical outcomes. It was important to know whether cartilage status at the time of surgery had a significant effect on failure rate in order to determine whether meniscal allograft transplantation is a reasonable surgical intervention for this challenging patient group. If the failure rates for patients with advanced cartilage damage were similar to patients with relatively preserved articular cartilage damage, it would be reasonable to include all patients in a definitive evaluation as it would increase the external validity of the study. Conversely, if failure rates were considerably higher in patients who most surgeons consider to be contraindicated to meniscal transplantation, a definitive evaluation should not include these patients. In this case, doing may compromise the trial by reducing the chance of showing a real benefit of meniscal allograft transplantation, if one existed, by diluting the effect size.
Therefore the primary objective of this study was to determine whether advanced cartilage damage at the time of surgery was a significant predictor of failure, independently of other potential risk factors. The secondary objectives were to determine whether other baseline variables were potential predictors of failure.

6.2 Materials and Methods

All patients undergoing meniscal allograft transplantation at UHCW between May 2005 and May 2014 were prospectively evaluated as part of an ongoing service evaluation by the knee team. The data for this study was anonymised by the knee team before the analysis was performed. The study was registered with the local Research and Development department of the hospital.

Patients were eligible for meniscal allograft transplantation if they were under fifty years of age and were experiencing pain, with a history of (sub)total meniscectomy in the same compartment of the knee. Each patient was assessed for suitability for meniscal allograft transplantation by combination of MRI, plain radiographs and arthroscopic images. Patients that had inflammatory arthritis or evidence of advanced joint arthrosis in compartments distinct from the recipient compartment were not offered meniscal allograft transplantation.
6.2.1 Assessment Protocol

Each patient was assessed and treated according to a joint restoration philosophy, where the optimal environment is created for the meniscal allograft transplantation. Firstly, clinical assessment of limb alignment was supplemented by weight bearing long leg alignment radiographs and secondly, assessment of knee stability was performed. If malalignment was present, proximal tibial opening wedge or distal femoral re-alignment osteotomy was performed to alter the weight bearing mechanical axis and reduce the forces across the affect compartment. Ligament stabilisation using hamstring autograft and biological chondral surface reconstructions were performed in addition to meniscal allograft transplantation, usually as simultaneous procedures along with osteotomy if limb malalignment was present. Chondral lesions were treated with debridement, microfracture or autologous chondrocyte transplantation using the MACI technique (Genzyme, Europe BV, Netherlands), depending on the lesion size.

The cohort was divided into three groups according to the International Cartilage Repair Society (ICRS) chondral grade\textsuperscript{217} of the affected compartment:

- **Group 1**: This group had up to ICRS grade 3a (partial thickness) chondral damage on one or both condylar surfaces.
- **Group 2**: This group had ICRS grade 3b (full thickness) or worse chondral damage on one condyle, with the opposite condylar surface having intact articular cartilage up to ICRS grade 3a.
- **Group 3**: This group had ICRS grade 3b (full thickness) or worse chondral damage to both condyles.
6.2.2 Surgical Technique

All procedures were performed using a minimally invasive arthroscopic technique with soft tissue fixation through bone tunnels. The technique was discussed in detail in the technique paper in press at the time of submission of this thesis (appendix D).

6.2.3 Rehabilitation

Patients were treated with a personalised, goal orientated physiotherapy program. The first six weeks of rehabilitation consisted of limited weight bearing to minimise the traction forces on the meniscal root anchor points. Early range of motion from 0 to 90° and active static quadriceps exercises were commenced with avoidance of open chain quadriceps exercises during the initial period. From six weeks, weight bearing, strengthening and proprioceptive rehabilitation was progressed once the patient achieved the required goals. From six months, a functional and sports specific rehabilitation program was undertaken with a return to normal activities from approximately nine months.

6.2.4 Outcomes

Failure was defined as complete removal of the allograft or conversion to joint replacement. The knee research team collected all outcomes data on patients.
6.2.5 Statistical analysis

Descriptive statistics were used to analyse the baselines demographics of the whole series as well as a breakdown by cartilage grade. Tests for significance on differences between cartilage groups were performed using the Chi squared test for categorical variables and ANOVA for continuous variables. Kaplan Meier survival curves were used for whole group survival and also survival according to cartilage grade. Cox regression (proportional hazards model) was performed to analyse for the effect on outcome of each potential predictor variable, independently of others. The proportional hazards assumption was tested by examining the log-log plots.

6.3 Results

There were 124 patients in the study period with a mean follow up of 3.25 (range 1 – 6) years. There were no patients lost to follow up for this cohort of patients. The mean age in this series was 30.9 (range 8 – 49) years. Table 6-1 shows the baseline demographics for the whole series and a breakdown by cartilage grade. Table 6-2 shows the additional procedures to address the cartilage lesion performed on patients with a full thickness lesion.
Table 6-1: Baseline demographics for the whole series and each group according to cartilage grade

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MAT</td>
<td>124</td>
<td>70</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>30.9</td>
<td>28.4</td>
<td>32.2</td>
<td>36.1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67.7</td>
<td>62.9</td>
<td>71.4</td>
<td>77.0</td>
</tr>
<tr>
<td>Time from meniscectomy to MAT in years</td>
<td>8.2</td>
<td>5.6</td>
<td>9.7</td>
<td>13.8</td>
</tr>
<tr>
<td>Mean age at meniscectomy (years)</td>
<td>23.6</td>
<td>23.2</td>
<td>23.9</td>
<td>24.4</td>
</tr>
<tr>
<td>Medial (%)</td>
<td>20.2</td>
<td>20.0</td>
<td>14.3</td>
<td>26.9</td>
</tr>
<tr>
<td>Cases with additional procedures performed at time of MAT (%)</td>
<td>56.5</td>
<td>38.6</td>
<td>74.1</td>
<td>84.6</td>
</tr>
<tr>
<td>Baseline IKDC scores</td>
<td>40.8</td>
<td>40.6</td>
<td>44.7</td>
<td>37.1</td>
</tr>
</tbody>
</table>

Table 6-2: Cartilage procedures performed at the time of meniscal allograft transplantation

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MAT</td>
<td>124</td>
<td>70</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Microfracture</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Chondrocyte implantation</td>
<td>12</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

The Kaplan-Meier allograft survival curve of the whole cohort is shown in Figure 6-1, with a six year survival of seventy per cent. The Kaplan-Meier allograft survival curve, grouped by cartilage grade is shown in Figure 6-2. This shows a 90%, 63% and 66% five year survival in groups one, two and three respectively, with the difference in survival rate for group one compared to groups two and three being
statistically significant (log-rank test significance 0.02). Table 6-3 shows the mean survival times for the whole group and each group by cartilage grade.

Table 6-3: Mean survival times (95% CI), grouped according to cartilage grade

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean survival (years)</th>
<th>95% confidence interval (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td>5.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Cartilage grade 1</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Cartilage grade 2</td>
<td>4.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Cartilage grade 3</td>
<td>4.9</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Figure 6-1: Whole group cumulative meniscal allograft survival
The results of the Cox regression model are shown in Table 6-4. When all other predictor variables are corrected for, only cartilage group was a statistically significant predictor of survival. When comparing individual groups, the probability of failure in group 3 was 11.49 times more likely than group 1 at any given time (95% CI, 1.6 – 81.0). There was a trend towards medial allografts predicting a worse outcome, but this was not statistically significant (p=0.07).
Table 6-4: Cox regression analysis of potential predictor variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage group (overall)</td>
<td>N/A</td>
<td>0.047</td>
<td>N/A</td>
</tr>
<tr>
<td>Cartilage group 3 (vs group 1)</td>
<td>11.49</td>
<td>0.01</td>
<td>1.6 – 81.0</td>
</tr>
<tr>
<td>Cartilage group 3 (vs group 2)</td>
<td>4.22</td>
<td>0.16</td>
<td>0.55 – 32.3</td>
</tr>
<tr>
<td>Baseline IKDC score</td>
<td>0.40</td>
<td>0.99</td>
<td>0.94 – 1.02</td>
</tr>
<tr>
<td>Lateral (vs Medial)</td>
<td>0.25</td>
<td>0.07</td>
<td>0.05 – 1.10</td>
</tr>
<tr>
<td>Male (vs female)</td>
<td>0.56</td>
<td>0.44</td>
<td>0.13 – 2.39</td>
</tr>
<tr>
<td>Additional procedures (vs isolated MAT)</td>
<td>1.65</td>
<td>0.51</td>
<td>0.37 – 7.41</td>
</tr>
<tr>
<td>Graft source (overall)</td>
<td>N/A</td>
<td>0.15</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at the time of MAT</td>
<td>0.99</td>
<td>0.91</td>
<td>0.9 – 1.1</td>
</tr>
</tbody>
</table>

6.4 Discussion

This study demonstrated that having a full thickness cartilage lesion at the time of meniscal allograft transplantation was a significant predictor of failure, despite attempts to improve the biomechanical environment of the knee. In this study, the overall survival of seventy per cent at six years hides the fact that within this there were significant differences depending on cartilage status at the time of transplantation. In an earlier study, using data from some of the same patients, advanced cartilage damage appeared to be associated with failure\(^{151}\). In this study with longer follow up, more patients and more events, cartilage group has been shown to be a strong predictor of failure, even when balancing for potential confounders. Further, the failure rate in patients with advanced cartilage damage on
a single surface appears to be similar to patients with advanced damage on both surfaces, despite the groups being different with respect to baseline characteristics. It has traditionally been considered that meniscal allograft transplantation is not suitable for patients with significant OA, leaving these patients with very few viable treatment options.

With more recent studies showing improved results, meniscal allograft transplantation is being performed in patients with advanced disease at some centres. Farr et al. performed combined autologous chondrocyte implantation in combination with meniscal allograft transplantation and had a fourteen per cent failure rate at a greater than two year follow up\textsuperscript{102}. Stone et al. reported a large series of patients having meniscal allograft transplantation in the presence of severe articular damage, reporting a failure rate of twenty per cent at a mean follow up of five years\textsuperscript{251}. They did not find an association between articular cartilage damage severity on Cox regression modelling, but all patients in the study already had severe articular cartilage damage. Other series report lower failure rates, although numbers are low\textsuperscript{35, 233}. This series showed worse failure rates in the presence of advanced cartilage damage, despite additional procedures to address the cartilage lesions.

It is interesting that the mean age at the time of meniscal allograft transplantation increases, but the time of initial meniscectomy is remarkably similar across all three cartilage groups. Although direct inferences cannot be drawn, it does appear that patients with advanced cartilage damage have similar characteristics to those with preserved articular cartilage, with the main difference being that they were late presenters. This is certainly plausible, given the known strong risk factor of
meniscectomy for OA. It is possible that earlier intervention in these patients may have a role preventing or delaying the advanced cartilage damage. However, there is currently not a role for performing meniscal allograft transplantation prophylactically as there is little direct evidence that it is chondroprotective, despite the evidence for the association between meniscectomy and OA being strong.

6.4.1 Limitations

One of the difficulties in comparing failure rates across studies is that failure is variably defined in the literature. Whilst complete allograft removal or conversion to joint replacement is a clear and hard failure definition, it does not directly take the patients’ symptoms into account. It has been suggested that low PROMs post-operatively could be included in the definition of failure. This would be likely to increase the failure rate of the series, but would have difficulties: Which measure would be used, would it take the patients pre-operative state into account, would an equal pre-operative and ten year post-operative score be considered a failure, given the likelihood of some OA progression in between?

This study only looked at survival rate and did not determine the clinical outcome for the groups using PROMs. Whilst this is important, a previous published study using some of the same patients has done this analysis. It determined that the clinical outcomes between patients with preserved cartilage and those with advanced cartilage damage were not significantly different. It is likely that the data were biased though, as patients that failed did not have PROMs scores collected. Since
these patients are likely to have worse scores and are more common in the group with advanced cartilage damage, this group is likely to appear better than it would if all data were collected. A further analysis of this data would also yield biased results, so it was decided that this would be unhelpful.

Finally, Cox regression modelling is able to balance for known (and measured) confounders. It cannot balance for unknown confounders, which may have had an influence on the results. Only a randomised controlled trial can balance unknown confounders.

6.5 Conclusion

Whilst the overall failure rate is similar to other studies reported in the literature, advanced chondral damage was a significant predictor of failure in this study. These findings support the traditional view that meniscal allograft transplantation has a worse outcome in patients with advanced cartilage damage. Therefore, patients with advanced cartilage damage were not included in the piloting phase due to the risk of reducing the overall effect size of the meniscal allograft transplantation intervention.
7 Meniscal Transplantation and Its Effect on Osteoarthritis Risk - MeTEOR: A Comprehensive Cohort Study Incorporating a pilot RCT – Protocol

Declarations

The randomisation sequence was created by Nick Parsons (statistician). The surgical intervention protocol was written with the help of Tim Spalding (surgeon). The personalised knee therapy protocol was written with the help of David Wright (physiotherapist). The MRI sequence protocol was created by Charles Hutchinson (radiologist).

Aspects of this chapter have been published:


Sponsorship

This study was jointly sponsored by the University of Warwick and University Hospitals Coventry and Warwickshire NHS Trust.

Ethics Committee approval date

3rd October 2013

NHS Research and Development approval date

22nd November 2013

Funding body

This research was supported by Arthritis Research UK (grant number 20149).
7.1 Introduction

Chapters two to five demonstrated that based on current knowledge, it is reasonable to consider that both meniscal allograft transplantation and physiotherapy might be effective treatments for patients with a symptomatic meniscal deficient knee. They have also demonstrated that there is an absence of definitive evidence to support one treatment over another, providing the basis for clinical equipoise between the treatments.

RCTs are the most reliable method of determining effectiveness and they are being increasingly used to assess complex interventions\textsuperscript{54, 75}. The second stage of the MRC framework for evaluating a complex intervention is the feasibility and piloting stage\textsuperscript{75}. This stage is often neglected, but is vital to identify problems that could undermine a definitive evaluation\textsuperscript{92}. Definitive evaluations of complex interventions can cost millions of pounds to perform; failure to adequately ensure a trial can be successfully performed is a waste of resources and ultimately unethical. Therefore, the primary aim was to perform a pilot study that would inform a potential definitive evaluation comparing meniscal allograft transplantation to physiotherapy for the treatment of patients with a symptomatic meniscal deficient knee. The objectives were:

- Assess the variability and distribution of the outcome measures, to provide an estimate of the treatment effects and inform a sample size calculation for a definitive evaluation.
• Identify issues with the trial study design including: Recruitment, retention, trial delivery and intervention fidelity.

7.2 Study Design

The study was a comprehensive cohort design with an embedded pilot RCT. Therefore there was a randomised arm and a parallel non-randomised preference group arm. The study was performed at a single UK centre (UHCW). Recruitment to randomised operative versus non-operative trials is notoriously difficult due to strong patient preferences.\textsuperscript{71, 270} Having a parallel preference group provided greater external validity as the overall recruitment rate was anticipated to be significantly higher.\textsuperscript{153} It may also increase the precision of the estimate of variability of the data.

7.3 Trial Summary and Flow Diagram

Patients between the ages of sixteen and fifty years presenting at the trial centre with pain in the affected compartment of the knee following a total or near total meniscectomy were potentially eligible to take part (see Figure 7-1 for details). Eligible patients were identified by the clinical team and then approached to enter the RCT arm by the chief investigator or research associates. If they agreed to enter, they were randomly allocated to an intervention. If patients were unwilling to be randomised but did wish to have either of the treatments being assessed in this study, they were asked whether they were willing to have their follow up information collected. Patients that did not want to be randomised but did wish to have follow up information collected had an MRI scan at baseline and twelve months as per
standard practice, as well as questionnaires at baseline, four, eight and twelve months.

Patients were randomised by the Warwick telephone randomisation service. This was produced and administered by Warwick Clinical Trials Unit.

The participants allocated to the operative group had a meniscal allograft transplantation and osteotomy if they had malalignment (defined below) of the knee and meniscal allograft transplantation only if they did not. The non-operative group had a personalised knee therapy programme and an offloading knee brace if they had malalignment of the knee and a personalised knee therapy programme only if they did not. Both the operative and non-operative treatments were used in this trust as standard care and the operating surgeons had extensive experience in performing the operations. MRI scans were performed at baseline (pre-intervention) and four, eight and twelve months post-intervention. The functional outcome data was collected using the KOOS, Lysholm and IKDC questionnaires at the same time points. These questionnaires were administered centrally by independent research associates. The participants were asked to provide details of any late complications or interventions related to their knee.
Figure 7-1: Trial participant flow diagram. Meniscal allograft transplantation (MAT), osteotomy (O)
7.4 Ethical Approval

This study was reviewed by the West Midlands – Solihull Research Ethics committee (Ref: 13/WM/0315). It was given ethical approval on the 3rd October 2013 (Appendix E). It was given local Research and Development approval on the 22nd November 2013 (Appendix F). The study was carried out in compliance with the Helsinki Declaration.

7.5 Study Registration

This study was registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN14194954) and the NIHR Comprehensive Research Network Portfolio (UKCRN ID15557).

7.6 Study Participants

Patients were eligible if they were between the ages of sixteen and fifty years with a symptomatic, meniscal-deficient compartment of the knee and the treating surgeon believed that the patient may benefit from meniscal allograft transplantation. These broad and pragmatic criteria were chosen to maximise the external validity of the results of the study.

Symptoms in the knee included pain, swelling or stiffness and could be present intermittently to be eligible. The amount of meniscal deficiency is difficult to
accurately quantify; it was left to the treating surgeon to decide whether there was
enough meniscal deficiency (loss) that the patient may benefit from meniscal allograft transplantation. The following guidance was used in the decision making process: A deficient meniscal rim providing no circumferential fibre support or an intact rim of less than two millimetres width over the majority of the meniscus. It was anticipated that meniscectomy due to trauma would be the most common reason for meniscal deficiency. Other meniscal pathologies were also eligible, for example previous excision of a discoid meniscus.

Patients were excluded if they had previous cartilage modifying procedures, such as microfracture or had significant exposed subchondral bone in the affected compartment due to arthritis (diagnosed on previous arthroscopy or MRI). These patients were excluded because chapter three demonstrated that most studies excluded these patients and chapter six demonstrated that advanced cartilage damage was a predictor of failure.

Patients that had contraindications to anaesthetic as well as patients where there was evidence that they would be unable to adhere to trial procedures were also excluded.

### 7.7 Recruitment

Patients were recruited from elective knee clinics at UHCW. When an eligible patient was identified by the treating surgeon, they were referred to the chief investigator or research associate.
7.8 Consent

The patients were informed about the RCT arm of the study and given a patient information sheet (PIS) specific to the pilot RCT (Appendix G). If patients were unwilling to have their treatment allocation decided by randomisation, they were given the opportunity to be part of the preference group (PG). A second PIS, which gave information about this follow up group was given to patients (Appendix G). This allowed participants to decide their treatment allocation but still be part of the study. Their data was collected at the same time points as the RCT arm, with the exception of not having MRI scans at four and eight months. Patients were offered as much time as they required to consider the study. Patients wishing to enter the study gave written consent (Appendix H). They were able to withdraw from the study at any time without prejudice.

7.9 Randomisation

Randomisation was by a computer generated sequence with a 1:1 allocation, stratified for ipsilateral limb malalignment. The Warwick Clinical Trials Unit secure telephone randomisation service was used to provide the participant allocation once the participant had consented to take part in the study. The allocated treatment was then reported back to the chief investigator and the treating surgeon.

7.10 Blinding

Participants could not be blinded to their treatment. The treating surgeons were of course not blind to the treatment, but did not take part in the post-operative
assessment of the participants; this was performed by a research associate blind to the treatment allocation. The MRI analysis was performed by IMorphics Ltd, Manchester UK; an independent medical image analysis company, who were blinded to the treatment allocation.

7.11 Study Interventions

7.11.1 Operative group

Participants usually had a general anaesthetic and femoral nerve block, but the attending anaesthetists were able to make the final decision based on the participants’ clinical requirements. Participants were in a supine position with a thigh side support. The surgery was performed by one of the knee surgeons competent in meniscal transplantation and osteotomies (TS or PT). There was no anticipated learning curve effect in this study as both participating surgeons performing the operations were proficient and experienced in the procedures. The meniscal allograft was frozen and sourced from one of two tissue banks: NHS Blood and Transplant Tissue Services, Liverpool UK, or Allosource, USA, imported by Joint Operations. These sources had been regularly used for meniscal allograft transplantation as standard practice at UHCW. The lack of availability from any one source required that multiple sources were used. The meniscal allograft was dissected from the tibial bone block, marking the topographical orientation. Number two non-absorbable sutures were inserted in the anterior and posterior horns using a Bunnell type stitch and an absorbable middle traction suture was inserted at the
anterior aspect of the popliteal hiatus laterally or at a point forty millimetres from the posterior horn medially.

Surgery was performed using an arthroscopic technique. The procedure started with a full assessment of the knee surfaces and the remaining amount of meniscal tissue. A two millimetre meniscal rim of tissue was maintained where possible. The meniscal bed was prepared to a fresh vascular margin before insertion of the allograft. Anterior and posterior meniscal root attachments were located and prepared using a shaver and rasp to expose bleeding bone. Guide wires were drilled from the anterior tibia to the insertion sites, maintaining a bone bridge on the tibia between the tunnels, and the guide wires were then over-drilled to create 4.5 mm tibial bone tunnels. Lead sutures were inserted through the tunnels and were retrieved through the arthroscopic portal.

The meniscal allograft sutures were fed through the lead sutures and the allograft was parachuted into place with the assistance of the middle traction suture. Fixation of the meniscal roots was achieved by tying the anterior and posterior horn lead sutures over the bone bridge on the anterior tibia. The meniscal rim was secured by placing multiple, vertical stacked mattress sutures around the anterior two thirds of the meniscus with an inside-out technique. The posterior third of the meniscus was secured with all-inside fixation devices, such as the Fast-Fix 360 (Smith and Nephew, Andover USA).

Participants were assessed for limb malalignment prior to randomisation, and then stratified accordingly. Participants in which the weight bearing line fell greater than five per cent from the centre of the tibial plateau, where 100% represents the total
tibial plateau width, were offered an osteotomy. A medial opening wedge high tibial osteotomy was performed for a varus proximal tibia and a medial closing wedge distal femoral osteotomy was performed for a valgus distal femur, subject to the surgeon’s preference and participant factors. In these procedures, the medial tibia or medial distal femur was exposed through a longitudinal incision and an oblique osteotomy was fashioned using image intensifier guidance. The final position was then held using a titanium locking plate and screws.

All participants randomised into the operative group received a standardised, written physiotherapy programme for their post-operative rehabilitation. Participants were advised to touch weight bear with crutches for six weeks, followed by progression to full weight bearing by eight weeks. Cycling exercises started at four weeks when 90 degrees bend had been achieved. Strength work started at three months and running was not allowed until nine months. Participants were advised of the risks of participating in contact sports and encouraged not to return to these activities in the long term.

7.11.2 Non-operative group

Participants had a personalised knee therapy course, specifically designed for patients with pain in a meniscal deficient knee. The course involved a personalised programme working on quadriceps control and strength, along with a core-strengthening programme, delivered over a minimum of three months. The initial assessment was performed by a senior knee physiotherapist, who gave a written booklet of exercise prescription, an exercise diary and an instruction list of common
exercises. If the participant wished to continue physiotherapy nearer their home, for example if they were not local to the area, they were referred for continued physiotherapy at a local unit. They were assessed at routine follow up clinics every four months, where adjustments to the personalised knee therapy could be made.

Participants with malalignment that were randomised to the non-operative group were also offered a size matched offloading knee brace.

7.12 Intervention Fidelity

Participants’ treatments in both the operative and non-operative groups were assessed for adherence to the trial protocols. In the operative group, the surgery and post-operative rehabilitation were reviewed by the chief investigator and a surgeon that was competent at performing meniscal allograft transplantation, but not directly involved in the treatment of trial participants (BP). A fidelity questionnaire was completed using the operative note and case report forms (Appendix I), with any disagreement resolved by discussion. All questions had to be answered in the affirmative for fidelity to be achieved.

In the non-operative group, the treatment fidelity was determined by the chief investigator and a senior physiotherapist able to deliver personalised knee therapy, but not directly involved in the treatment of trial participants (IH). A fidelity questionnaire was completed using the physiotherapy case report form and examination of UHCW physiotherapy records, as well as communication with the physiotherapists at UHCW (Appendix I) with any disagreement resolved by
discussion. All questions had to be answered in the affirmative for fidelity to be achieved.

7.13 Outcome Measures

The primary endpoint was the mean change in cartilage volume in the central weight bearing portion of the affected compartment of the knee at one year post-intervention. The change in cartilage volume was also evaluated at four and eight months following the intervention. All participants were scanned on a General Electric MRI scanner using T2 gradient Echo sequences with the same protocol (Appendix J), performed by MRI trained research staff at UHCW. The scans were then anonymised and sent to IMorphics for analysis. IMorphics are a UK based world leading image analysis company with over twenty years expertise in the area. They use advanced and proprietary modelling software to automatically identify the bone edges of the knee. The principle is similar to facial recognition software, where an active appearance model is built using a training set of images, which is made up of a dense set of anatomical correspondence points (over 30 000 in the knee). The model is then able to identify valid new shapes and appearances, so it can be applied to previously unseen images. This method has been shown to be one of the best to automatically segment images, with mean positional errors of the correspondence points of less than one millimetre. They have also published test-retest variabilities for manual cartilage volume and thickness measurements, which compare favourably to other published studies in the knee.
IMorphics reputation as world leaders in biomedical image analysis has been further established by winning the Medical Image Computing and Computer Assisted Intervention (MICCAI) Grand Challenge on a number of occasions for image analysis on previously unseen images. This is a highly prestigious international biomedical image analysis competition with academic and commercial groups competing. One previous win included segmenting the knee bone and cartilage.

IMorphics are a successful commercial company and their image analysis technologies and services are used by medical implant companies to perform three-dimensional modelling. The cost of their services would normally be too high for this project, but due to academic links and previous successful collaborations with one of the supervisors of this project (Charles Hutchinson), IMorphics agreed to offer their services at much lower academic rates. Therefore it was possible to use their services.

Cartilage was manually segmented by a single operator that had previously passed IMorphic’s training test (repeatedly segmenting parts of the knee with an intra-observer coefficient of variation of less than three per cent), using IMorphic’s proprietary software\textsuperscript{134}. Cartilage segmentations were also reviewed by a senior segmenter for consistency. The bone was automatically segmented using active appearance models. This semi-automated segmentation is IMorphics standard image analysis protocol and the previously published data comes from this protocol.

The central portion of each compartment of the tibiofemoral joint is commonly used to determine cartilage change in studies\textsuperscript{87, 134, 283} for two main reasons: Firstly, it has
been shown that global cartilage change is small and can mask rapid regional changes. This may particularly be expected in patients with a previous meniscectomy where high central stresses and low peripheral stresses in the knee may lead to rapid central loss and potentially peripheral cartilage volume gain. Secondly, the peripheral edge of cartilage is the most difficult region to segment and therefore most prone to measurement error. It has been shown that the coefficient of variation decreases if the edges of cartilage are trimmed\(^{283}\). The central area of the affected compartments of the femoral condyle and tibial plateau (medial or lateral) were identified using a dense set of anatomically consistent correspondence points, based on the meniscal window in the mean knee on the previously developed model. Figure 7-2 illustrates the meniscal window for the tibial plateau of the medial compartment. This method allows the central weight bearing area to be consistently determined and has been shown to have a mean positional error of around one millimetre\(^{285}\). The cartilage volume in these regions was then measured and change between baseline and follow up time points was calculated.
The secondary outcome measures included the KOOS$^{227}$, Lysholm score$^{176}$, IKDC score$^{128}$, mean change in cartilage thickness, bone shape change and complications. Cartilage thickness was identified using the same methods as described for cartilage volume and the same regions of interest were used. Multiple thickness measurements were taken within the region of interest and a mean thickness was then calculated. Bone shape change has shown promise as a sensitive method of identifying progression of OA$^{47}$. The change in surface area of the affected tibiofemoral compartment was calculated from the automated bone segmentation.

### 7.14 Follow-up

In the RCT arm of the study, participants had MRI scans at baseline and then four, eight and twelve months post-intervention. In the preference group arm, the participants had MRI scans at baseline and at twelve months post-intervention. It
was the intention that all participants completed questionnaires at all time points (baseline, four, eight and twelve months).

The follow up points were post-intervention, rather than post-randomisation. It was considered that more meaningful MRI data would be achieved using these time points if there was a long delay to surgery for participants. It would also mean that follow up appointments and MRI scans could be linked to standard clinical appointments and MRI scans, reducing the inconvenience for participants and potentially reducing loss to follow up. All participants completed questionnaires on the day of entry to the study and most had MRI scans, according to clinical need. If the intervention was started within four months of the day of entry into the study, the MRI and questionnaire were used as baseline scores. If the start of the intervention exceeded four months, an MRI scan and new questionnaire was completed as close to the start of the intervention as possible, in the RCT arm. In the preference group arm the MRI scan was not repeated, as this did not constitute routine follow up.

In the first instance, a research associate that was blinded to the treatment allocation collected all functional outcome scores from the participants in person. If a participant missed the appointment or was not willing to attend, the outcomes pack was sent out by post and the participant was telephoned. If the research associate was unable to obtain this information within four weeks of the time point for collection, the information was deemed missing. Further data was collected at later time points as originally planned.
7.15 Post Recruitment Withdrawals and Exclusions

Participants were able withdraw from the trial at any time. If a participant decided to have a different treatment to which they were randomised, they were followed up wherever possible and data was collected as per the protocol until the end of the trial. Participants could be withdrawn from the study by the chief investigator at any time if any safety concerns arose.

During the study it became clear that the delay to surgery was a larger issue than anticipated. No time point for withdrawing participants from the study had been decided prospectively, but it was decided at a trial management group (TMG) meeting that if a participant had not started the intervention at one year following randomisation, they should be withdrawn from the study. It was decided that this factor was an important finding in itself and that the study had to have a defined end point.

For the purposes of the thesis, it was decided that if participants in the RCT arm had a delay to starting the intervention of greater than four months following the end of the recruitment period, submission of the thesis would not include their completed follow up. If there was a delay of over two months in the preference group following the end of the recruitment period, submission of the thesis would not include their completed follow up. This was decided for logistical reasons of completing a PhD within the maximum allowed time out of programme from clinical training. Follow up outcomes in these participants will continue to be collected following the submission of the thesis.
There were no previously performed similar studies so there was no way of gaining a meaningful standardised effect size. Therefore this study was a pilot and no formal power calculation was performed. The recruitment period was twelve months and it had been estimated that eighteen patients would be entered into the randomised arm of the trial, based on a fifty per cent recruitment rate. A sample size of eighteen had been chosen for a combination of being able to deliver the study within the timeframe of a PhD and the expectation that it would provide enough information to achieve the objectives of the study. It was anticipated that a sample size of eighteen participants would provide some guidance as to the likely size of the treatment effect and would allow nuisance parameters such as the variability (standard deviation) in the primary outcome to be estimated with some precision. Whilst it has been recommended that twelve participants per group would be appropriate for pilot studies, it was anticipated that cartilage volume change would have a small variability. This would allow a similarly precise estimate with relatively fewer participants. If appropriate, the preference group outcomes could be combined with the RCT to increase the precision of the estimate of variability.

It was expected that the vast majority of patients that did not want to be randomised would wish to be part of the preference group, as the burden on participants was not different from routine clinical care. Therefore it was estimated that between fourteen and eighteen participants would enter the preference group arm of the study.
7.17 Data Management

The case report forms were designed by the chief investigator in conjunction with the trial management team. All electronic patient-identifiable information was held on a secure, password-protected database accessible only to essential personnel. Paper forms with patient-identifiable information were held in secure, locked filing cabinets within a restricted area of the Clinical Sciences Research Laboratories. Patients were identified by a code number only. Direct access to source data was required for trial-related monitoring. All paper and electronic data will be retained for at least five years after completion of the trial.

7.18 Statistical Analysis

The main analysis investigated the differences in the outcome measures between the treatment groups on an intention-to-treat basis, at twelve months post-intervention. As this was a pilot study, the main analysis was exploratory in nature, to assess the size and direction of observed differences between the two treatment groups, and the variability and distribution of the outcome measures at each assessment occasion. Changes in PROMs were assessed for approximate normal distribution and presented with means and standard deviations unless histograms showed a strongly non-normal distribution. Baseline data was summarised to check for comparability between treatment arms. The changes in outcome measures for the intervention and comparator groups were presented in their individual arms (RCT and preference group) as well as combined for the four, eight and twelve month time points. This was a relatively small study, so group means were unlikely to be estimated with much precision. However, the statistical significance of difference in outcomes
between treatment groups were formally assessed using independent samples t-tests at twelve months. Tests were two-sided and considered to provide evidence for a significant difference if p-values were less than 0.05 (5% significance level). Levene’s test for equality of variances was also performed to determine whether equality of variances could be assumed for each outcome measure. Differences between the RCT and preference groups were explored and if appropriate, RCT and preference group data was merged for an analysis of the whole cohort, as well as an analysis of the RCT group alone.

The MRI measures (cartilage volume, cartilage thickness and bone shape change) were logarithm transformed (natural logarithms) to improve the distributional properties of approximate normality, prior to analysis. Both the baseline and twelve month scores were logarithm transformed and the baseline was subtracted from the twelve month score. The significance of differences in means between groups was tested on this scale using two sided independent samples t-tests. The mean log-ratio and 95% confidence intervals were transformed back to the original (natural) scale by taking antilogarithms and expressed as a per cent change by subtracting one and multiplying by 100.

Pooled standard deviations for the change in outcome measures from baseline to twelve months were calculated by taking the root mean square of the standard deviations for each outcome measure, to allow sample size calculations for a full RCT to be performed\(^{67,231}\). This was performed on the RCT data and the combined RCT and preference group data.
8 Meniscal Transplantation and Its Effect on Osteoarthritis Risk - McTEOR: A Comprehensive Cohort Study Incorporating a pilot RCT – Results

Declarations

Research associates collected questionnaires from participants. All other trial procedures were carried out by the candidate.

Aspects of this chapter have been presented:


Research, Development and Innovation Summit, University Hospitals Coventry and Warwickshire UK. Meniscal Transplantation and its Effect of Osteoarthritis Risk: A Pilot Randomised Trial. (Poster)

Sponsorship

This study was jointly sponsored by the University of Warwick and University Hospitals Coventry and Warwickshire NHS Trust.
8.1 Objectives

The objectives of this study were:

- Assess the variability and distribution of the outcome measures, to provide an estimate of the treatment effects and inform a sample size calculation for a definitive evaluation.

- Identify issues with the trial study design including: Recruitment, retention, trial delivery and intervention fidelity.
8.2 Recruitment and follow up

Recruitment took place between November 2013 and November 2014. There were a total of thirty-six participants recruited, of which twenty-one were in the RCT arm and fifteen in the preference group arm. Figures 8-1 to 8-3 show the recruitment rate for the whole group, the RCT and the preference group arms respectively. The expected recruitment total of thirty-six, with eighteen in the RCT arm was similar to the actual recruitment rate, with a slightly preferential split of fifty-eight per cent to forty-two per cent in favour of the RCT, compared to the preference group arm respectively. Considering all eligible patients, the RCT recruitment rate was fifty-five per cent, which equates to a monthly recruitment rate of 1.75 participants. The chief investigator recruited all participants.

Figures 8-4 and 8-5 are flow diagrams of participants through the RCT and preference group arms of the study respectively. A total of fifteen patients were excluded after screening. The most common reasons for exclusion were: A patient needing further concurrent surgery, and the surgeon not believing the patient would benefit from meniscal allograft transplantation. Only two patients declined to take any part in the study, both giving reasons of not living near the hospital and not wanting to commit to follow up.
Figure 8-1: Trial recruitment compared to predictions for the whole cohort

Figure 8-2: Trial recruitment compared to predictions for the RCT arm of the study
Figure 8-3: Trial recruitment compared to predictions for the preference group (PG) arm of the study

Three participants that were randomised to meniscal allograft transplantation were withdrawn from the study at one year, as they had not received the intervention by that time point. At the time of being withdrawn, two of the participants had not been allocated an allograft and the other had not been allocated a date for surgery.

Two participants in the personalised knee therapy preference group were lost to follow up before the four month data points were collected. One participant left the country for work reasons and the other had decided to pursue the surgical intervention privately and did not wish to remain in the study in any form.

Two participants missed their four month follow up appointments, one in the RCT surgical group and one in the RCT personalised knee therapy group. Both participants did not attend scheduled appointments and were unable to commit to rescheduling due to work commitments at the time.
Two participants that were randomised to meniscal allograft transplantation had not completed follow up at the time of submission of this thesis, as they had surgery over four months following the end of the recruitment period. The delay from entering the study to surgery was five months for one participant and nine months for the other. In the preference group, two participants in the meniscal allograft transplantation group had not completed follow up at the time of submission. The delay from entering the study to surgery was two months for one participant and five months for the other. There were no other missing data points or losses to follow up.

One participant in the personalised knee therapy preference group decided to proceed with meniscal allograft transplantation within the follow up period of the study, due to family reasons. That participant had completed the course of personalised knee therapy before surgery and remained in the study.
Figure 8-4: Flow diagram of participants through the RCT arm of the study

Assessed for eligibility (n=51)

- Excluded (n=15)
  - Needed other surgery (n=4)
  - Surgeon decision (n=4)
  - Microfracture (n=1)
  - Too young (n=1)
  - Severe OA (n=3)
  - Patient declined (n=2)

- Entered RCT (n=21)

Allocated MAT (n=10)
- Malalignment (n=3)
- Received intervention (n=7)
- Protocol violation (n=0)

Allocated PKT (n=11)
- Malalignment (n=3)
- Received intervention (n=11)
- Protocol violation (n=0)

Loss to follow up:
- Withdrawn (n=3)
- Missing 4 month outcome (n=1)

Loss to follow up:
- Withdrawn (n=0)
- Missing 4 month outcome (n=1)

Analysed:
- Baseline (n=10)
- 4 months (n=6)
- 8 months (n=6)
- 12 months (n=5)

Analysed:
- Baseline (n=11)
- 4 months (n=10)
- 8 months (n=11)
- 12 months (n=11)
The baseline demographics of the groups are shown in Table 8-1 and baseline outcome scores are shown in Tables 8-2 to 8-3. Baseline demographics appear to be approximately comparable, although it is difficult to make comparisons with a small sample. Possible small imbalances in the RCT groups included more smokers and a higher body mass index (BMI) in the meniscal allograft transplantation RCT group.

In the preference groups, possible small imbalances included an older mean age and longer time from injury to assessment in the meniscal allograft transplantation group,
whereas there was a higher BMI and a higher number of participants with malalignment in the personalised knee therapy group.

Baseline MRI values appear closely matched between the RCT groups, and there were no major imbalances between any of the other groups. According to the protocol, baseline MRI scans and PROMs collected close to the day of randomisation from participants in the RCT arm were only valid if they were within four months of the start of the intervention. This was the case for all participants in the personalised knee therapy group but six participants in the meniscal allograft transplantation group had repeated baseline PROMs (five MRI scans). There was a trend towards a small worsening of PROMs in the repeated baseline measures, with all KOOS sub-domains, the KOOS$_4$ composite and IKDC scores being lower (Lysholm score was the same). There were no major changes in the MRI outcomes between the two baseline time points.

The main baseline imbalance between the RCT groups was that meniscal allograft transplantation group had worse scores in all KOOS sub-domains, except Symptoms. This does not appear to be matched in other PROMs scores, as the IKDC score was worse in the personalised knee therapy RCT group than the meniscal allograft transplantation group; Lysholm scores were similar. The baseline preference group KOOS scores appear to be more closely aligned with the personalised knee therapy RCT group.
### Table 8-1: Baseline demographics for the four groups

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=10)</td>
<td>PKT (n=11)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>27.5 (9.7)</td>
<td>27.5 (7.3)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>10/0</td>
<td>8/3</td>
</tr>
<tr>
<td>Left/Right</td>
<td>2/8</td>
<td>6/5</td>
</tr>
<tr>
<td>Medal/Lateral meniscectomy</td>
<td>1/9</td>
<td>3/8</td>
</tr>
<tr>
<td>Normal/Malalignment</td>
<td>7/3</td>
<td>7/4</td>
</tr>
<tr>
<td>Smoker – Y/N</td>
<td>3/7</td>
<td>0/11</td>
</tr>
<tr>
<td>Alcohol Low/Mod/High</td>
<td>5/3/1/1</td>
<td>8/3/0/0</td>
</tr>
<tr>
<td>Initial injury mechanism</td>
<td>Sport: 9 Other trauma: 1</td>
<td>Sport: 10 Other trauma: 1</td>
</tr>
<tr>
<td>Under three previous knee operations</td>
<td>5 of 10</td>
<td>4 of 11</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>26.6 (2.8)</td>
<td>23.1 (3.1)</td>
</tr>
<tr>
<td>Mean time from initial injury to assessment for transplant in years (SD)</td>
<td>7.6 (7.3)</td>
<td>7.7 (3.3)</td>
</tr>
<tr>
<td>Median time from randomisation to treatment in days (Interquartile range)</td>
<td>198 (152 – 548)</td>
<td>35 (4 – 44)</td>
</tr>
<tr>
<td>Surgeon performing MAT</td>
<td>TS: 7</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT using ‘day of randomisation’ MRIs (n=10)</td>
<td>MAT (n=10)</td>
</tr>
<tr>
<td>Cartilage volume (mm³)</td>
<td>2705 (632)</td>
<td>2848 (723)</td>
</tr>
<tr>
<td>Cartilage thickness (mm)</td>
<td>2.02 (0.48)</td>
<td>2.00 (0.39)</td>
</tr>
<tr>
<td>Bone shape (mm²)</td>
<td>3375 (360)</td>
<td>3362 (380)</td>
</tr>
</tbody>
</table>
Table 8-3: Baseline PROMs, presented as mean (standard deviation) for each group in the RCT, preference group and combined RCT and preference group arms

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT using ‘day of</td>
<td>MAT (n=10)</td>
<td>MAT (n=6)</td>
</tr>
<tr>
<td></td>
<td>randomisation’</td>
<td>PKT (n=11)</td>
<td>PKT (n=9)</td>
</tr>
<tr>
<td></td>
<td>scores (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>57.85 (8.38)</td>
<td>56.07 (11.67)</td>
<td>58.93 (17.02)</td>
</tr>
<tr>
<td></td>
<td>56.07 (12.46)</td>
<td>60.07 (12.68)</td>
<td>61.90 (17.46)</td>
</tr>
<tr>
<td></td>
<td>57.14 (13.43)</td>
<td>60.89 (14.63)</td>
<td></td>
</tr>
<tr>
<td>KOOS pain</td>
<td>51.11 (14.42)</td>
<td>49.44 (15.26)</td>
<td>58.80 (18.63)</td>
</tr>
<tr>
<td></td>
<td>68.69 (13.33)</td>
<td>69.75 (20.95)</td>
<td>52.95 (16.65)</td>
</tr>
<tr>
<td></td>
<td>64.11 (16.69)</td>
<td>52.95 (16.69)</td>
<td></td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>64.4 (12.16)</td>
<td>58.24 (13.57)</td>
<td>75.25 (14.63)</td>
</tr>
<tr>
<td></td>
<td>85.56 (14.50)</td>
<td>77.61 (21.29)</td>
<td>64.61 (15.94)</td>
</tr>
<tr>
<td></td>
<td>64.11 (16.69)</td>
<td>81.99 (17.83)</td>
<td></td>
</tr>
<tr>
<td>KOOS sports</td>
<td>25.5 (12.35)</td>
<td>24.00 (11.01)</td>
<td>38.33 (23.80)</td>
</tr>
<tr>
<td></td>
<td>49.46 (25.93)</td>
<td>46.11 (30.60)</td>
<td>29.38 (17.69)</td>
</tr>
<tr>
<td></td>
<td>29.38 (27.41)</td>
<td>48.00 (17.83)</td>
<td></td>
</tr>
<tr>
<td>KOOS QoL</td>
<td>16.25 (13.88)</td>
<td>15.63 (14.21)</td>
<td>34.38 (17.57)</td>
</tr>
<tr>
<td></td>
<td>27.27 (17.06)</td>
<td>43.75 (22.75)</td>
<td>22.66 (17.66)</td>
</tr>
<tr>
<td></td>
<td>34.69 (21.02)</td>
<td>34.69 (21.02)</td>
<td></td>
</tr>
<tr>
<td>KOOS composite</td>
<td>37.68 (7.68)</td>
<td>36.28 (9.38)</td>
<td>47.60 (16.49)</td>
</tr>
<tr>
<td></td>
<td>40.53 (17.07)</td>
<td>53.19 (17.07)</td>
<td></td>
</tr>
<tr>
<td>IKDC</td>
<td>54.46 (16.37)</td>
<td>52.89 (17.70)</td>
<td>55.22 (16.61)</td>
</tr>
<tr>
<td></td>
<td>48.58 (12.91)</td>
<td>57.01 (16.56)</td>
<td>53.76 (16.77)</td>
</tr>
<tr>
<td></td>
<td>53.76 (14.89)</td>
<td>52.38 (14.89)</td>
<td></td>
</tr>
<tr>
<td>Lysholm</td>
<td>57.90 (17.93)</td>
<td>57.90 (18.17)</td>
<td>64.60 (16.20)</td>
</tr>
<tr>
<td></td>
<td>58.73 (11.05)</td>
<td>69.11 (17.23)</td>
<td>60.38 (17.22)</td>
</tr>
<tr>
<td></td>
<td>63.40 (14.71)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.3  Trial delivery

8.3.1 Delay to surgery

In the pilot RCT, there were large differences between the groups in the delay from randomisation to the start of the intervention (Table 8-1). The median delay to treatment was thirty-five days in the personalised knee therapy group and no participants had a delay of four months or greater. In contrast, the median time from randomisation to meniscal allograft transplantation was 198 days. In the RCT group, five participants waited over six months before having surgery; a further three waited for one year before being withdrawn from the study. Although the breakdown in time delay was not collected, the majority of the delay for participants waiting
over four months was the allocation of an appropriately sized allograft. There were five participants in the meniscal allograft transplantation preference group that had surgery within four months.

8.3.2 Audit by the study co-sponsors

The study was audited by the co-sponsors (University of Warwick and UHCW NHS Trust) on the 13th August 2014, during the recruitment phase. A copy of the report is in Appendix K. There were no major or moderate adverse findings and the study documentation was found to be kept to a good standard.

8.3.3 Trial Management Group meetings

Trial Management Group (TMG) meetings started in February 2014, once recruitment had started. They were initially held every three months, which was then extended to every four months once recruitment was on target. These meetings were used to resolve issues during the study that had not been anticipated beforehand, as well as the development of the chief investigator’s research related skills. Issues that were discussed included: Recruitment targets and strategies, research associate cover, discussion of delays to surgery and withdrawals.

8.3.4 Intervention fidelity

Fidelity of the interventions was determined by the chief investigator and an independent expert (surgeon or physiotherapist, depending on the intervention), with the help of the fidelity questionnaires (Appendix I). Participants were classified as
having had intervention fidelity if all questions were answered in the affirmative. In the meniscal allograft transplantation treatment groups, all thirteen participants that had surgery were classified as having had intervention fidelity. The median number of rehabilitation sessions amongst participants that had surgery was five (range of three to thirteen). In the personalised knee therapy treatment groups, eighteen of twenty participants were classified as having had intervention fidelity. Of the two participants that did not have fidelity, one was from the RCT arm and the other was from the preference group arm. One participant did not attend organised physiotherapy sessions and the other decided to withdraw from physiotherapy in favour of going on the waiting list for meniscal allograft transplantation. The median number of physiotherapy sessions amongst participants having personalised knee therapy was 4.5 (range 1 – 18) over a median of 7 months (range 0 – 12 months).

8.3.5 MRI measures

Tables 8-4 to 8-6 show the percentage change of the different MRI measures from baseline to four, eight and twelve months in the RCT arm of the trial respectively. These results are graphically illustrated in Figures 8-6 to 8-8. Table 8-6 also shows the percentage change from baseline to twelve months in the preference groups and combined RCT and preference group arms, which is graphically illustrated in Figures 8-9 to 8-11. Table 8-7 shows the significance testing for the change MRI outcome measures at twelve months. There were no statistically significant differences between the groups for any measure.
Table 8-4: Change in MRI outcome measures from baseline to four months in the RCT arm. Presented as mean (standard deviation) percentage change

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=6)  PKT (n=10)</td>
</tr>
<tr>
<td>Cartilage volume</td>
<td>-19.53 (20.65)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-7.81 (22.27)</td>
</tr>
<tr>
<td>Cartilage thickness</td>
<td>-14.56 (27.65)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-6.90 (16.36)</td>
</tr>
<tr>
<td>Bone shape</td>
<td>-3.38 (6.08)</td>
</tr>
<tr>
<td>(% change)</td>
<td>0.07 (5.33)</td>
</tr>
</tbody>
</table>

Table 8-5: Change in MRI outcome measures from baseline to eight months in the RCT arm. Presented as mean (standard deviation) percentage change

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=6)  PKT (n=11)</td>
</tr>
<tr>
<td>Cartilage volume</td>
<td>-12.40 (24.03)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-8.46 (12.33)</td>
</tr>
<tr>
<td>Cartilage thickness</td>
<td>-11.18 (19.22)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-6.90 (11.14)</td>
</tr>
<tr>
<td>Bone shape</td>
<td>-9.58 (10.44)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-0.29 (5.11)</td>
</tr>
</tbody>
</table>

Table 8-6: Change in MRI outcome measures from baseline to twelve months for each group in the RCT, preference group and combined RCT and preference group arms. Presented as mean (standard deviation) percentage change

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=5)  PKT (n=11)</td>
<td>MAT (n=4)</td>
<td>PKT (n=7)</td>
</tr>
<tr>
<td>Cartilage volume</td>
<td>-8.72 (16.63)</td>
<td>-13.47 (19.54)</td>
<td>-17.69 (17.75)</td>
</tr>
<tr>
<td>(% change)</td>
<td>-7.64 (14.09)</td>
<td>-6.88 (11.94)</td>
<td>-16.62 (14.40)</td>
</tr>
<tr>
<td>Cartilage thickness</td>
<td>-10.51 (23.91)</td>
<td>-2.64 (7.13)</td>
<td>-11.39 (16.58)</td>
</tr>
<tr>
<td>(% change)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 8-6: Mean percentage and standard deviation change for cartilage volume at four, eight and twelve months. Note a negative number represents a loss

Figure 8-7: Mean percentage and standard deviation change for cartilage thickness at four, eight and twelve months. Note a negative number represents a loss
Figure 8-8: Mean percentage and standard deviation change for bone shape at four, eight and twelve months. Note a negative number represents a loss.

Figure 8-9: Mean percentage and standard deviation change for cartilage volume in each group in: The RCT, preference group and combined RCT and preference group arms.
Figure 8-10: Mean percentage and standard deviation change for cartilage thickness in each group in: The RCT, preference group and combined RCT and preference group arms

Figure 8-11: Mean percentage and standard deviation change for bone shape in each group in: The RCT, preference group and combined RCT and preference group arms
Table 8-7: Significance testing results for percentage change in the MRI outcomes from baseline to twelve months in: The RCT, and combined RCT and preference group arms. A positive mean and confidence interval represents a higher number in the meniscal allograft transplantation group

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Cartilage volume</td>
<td>5.48 (-13.53 – 28.67)</td>
<td>0.556</td>
</tr>
<tr>
<td>Cartilage thickness</td>
<td>-0.83 (-13.54 – 13.75)</td>
<td>0.899</td>
</tr>
<tr>
<td>Bone shape change</td>
<td>-8.08 (-20.78 – 6.65)</td>
<td>0.233</td>
</tr>
<tr>
<td></td>
<td>-3.72 (-17.72 – 12.67)</td>
<td>0.624</td>
</tr>
<tr>
<td></td>
<td>-8.73 (-18.15 – 1.77)</td>
<td>0.096</td>
</tr>
<tr>
<td></td>
<td>-8.13 (-19.99 – 5.53)</td>
<td>0.223</td>
</tr>
</tbody>
</table>

Table 8-8 shows the pooled standard deviations for change in MRI outcomes at twelve months post-intervention. The pooled standard deviations for the primary outcome measure, cartilage volume change, were 18.14 and 19.71 for the RCT and combined RCT and preference group arms respectively.

Table 8-8: Pooled standard deviations for percentage change in MRI outcomes from baseline to twelve months in: The RCT and the combined RCT and preference group arms

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage volume</td>
<td>18.14</td>
<td>19.71</td>
</tr>
<tr>
<td>Cartilage thickness</td>
<td>13.06</td>
<td>10.55</td>
</tr>
<tr>
<td>Bone shape change</td>
<td>17.64</td>
<td>14.56</td>
</tr>
</tbody>
</table>
Table 8-9 shows significance testing of the baseline differences between the RCT and preference groups. There was a trend towards higher PROMs in the meniscal allograft transplantation preference group, compared to the meniscal allograft transplantation RCT group but this was only statistically significant in the KOOS activities of daily living (ADLs) and Quality of Life (QoL) sub-domains and not the composite score, or other PROMs. Differences between the personalised knee therapy groups were not statistically significant. When combining the RCT groups and comparing them to the combined preference groups, there was also a trend towards higher PROMs in the preference groups but this was not statistically significant, except for the KOOS QoL sub-domain.

Table 8-9: Significance testing for differences between the RCT and preference groups. Note all PROMs below range from 0 to 100, with 100 being the highest achievable score. KOOS4 is a composite score made up of the average of all KOOS sub-domains, except ADLs. Note a positive mean difference favours the preference group scores being higher.

<table>
<thead>
<tr>
<th></th>
<th>MAT</th>
<th>PKT</th>
<th>Combined RCT and preference group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>P value</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>2.86 (-12.45 – 18.16)</td>
<td>0.695</td>
<td>1.839 (-12.33 – 16.01)</td>
</tr>
<tr>
<td>KOOS Pain</td>
<td>9.35 (-8.97 – 27.67)</td>
<td>0.292</td>
<td>1.07 (-15.12 – 17.25)</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>17.01 (0.63 – 33.39)</td>
<td>0.043</td>
<td>-7.95 (-24.79 – 8.89)</td>
</tr>
<tr>
<td>KOOS Sports</td>
<td>14.33 (-10.63 – 39.30)</td>
<td>0.212</td>
<td>-3.43 (-29.97 – 23.10)</td>
</tr>
<tr>
<td>KOOS QoL</td>
<td>18.75 (1.59 – 35.91)</td>
<td>0.034</td>
<td>16.48 (-2.21 – 35.17)</td>
</tr>
<tr>
<td>KOOS4 composite</td>
<td>11.32 (-2.41 – 25.05)</td>
<td>0.099</td>
<td>3.99 (-12.45 – 20.43)</td>
</tr>
<tr>
<td>IKDC</td>
<td>2.33 (-16.86 – 21.51)</td>
<td>0.798</td>
<td>7.99 (-5.65 – 21.64)</td>
</tr>
<tr>
<td>Lysholm</td>
<td>6.60 (-12.77 – 25.98)</td>
<td>0.477</td>
<td>10.47 (-2.92 – 23.87)</td>
</tr>
</tbody>
</table>
Table 8-10 to 8-12 show the changes in PROMs from baseline to four, eight and twelve months respectively in the different groups. Figure 8-12 to 8-19 graphically demonstrate the changes in scores at the different time points. PROMs scores improved over time in the meniscal allograft transplantation group, whereas a progression in the personalised knee therapy group was not clear. Table 8-13 shows the mean differences and significance testing of the various groups. In the RCT, the differences between the groups were not statistically significant except the KOOS ADLs sub-domain (p=0.029), although the KOOS₄ composite score was approaching significance (p=0.054). When combining the RCT and preference group participants the improvement in the meniscal allograft transplantation group was significant in the KOOS₄ composite score and all the KOOS sub-domains except Sports (p=0.055). The differences were also close to, but did not reach, statistical significance in the IKDC (p=0.062) and Lysholm (p=0.103) scores.

Table 8-10: Change in PROMs from baseline to four months. Presented as mean (standard deviation) for each group in the RCT, preference group and combined RCT and preference group arms

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=6)</td>
<td>PKT (n=10)</td>
<td>MAT (n=6)</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>7.74 (13.25)</td>
<td>8.21 (13.58)</td>
<td>-4.29 (31.35)</td>
</tr>
<tr>
<td>KOOS Pain</td>
<td>5.56 (20.86)</td>
<td>14.72 (12.15)</td>
<td>6.48 (25.13)</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>10.29 (17.25)</td>
<td>2.50 (18.99)</td>
<td>3.92 (17.52)</td>
</tr>
<tr>
<td>KOOS Sports</td>
<td>-6.67 (15.38)</td>
<td>4.00 (34.86)</td>
<td>-5.83 (14.63)</td>
</tr>
<tr>
<td>KOOS QoL</td>
<td>11.45 (11.47)</td>
<td>5.00 (7.68)</td>
<td>0.00 (24.69)</td>
</tr>
<tr>
<td>KOOS₄ composite</td>
<td>4.52 (9.69)</td>
<td>7.98 (11.39)</td>
<td>-0.91 (21.98)</td>
</tr>
<tr>
<td>IKDC</td>
<td>1.75 (9.52)</td>
<td>4.68 (11.47)</td>
<td>-10.88 (20.92)</td>
</tr>
<tr>
<td>Lysholm</td>
<td>-3.67 (19.18)</td>
<td>14.60 (10.89)</td>
<td>-4.83 (27.38)</td>
</tr>
</tbody>
</table>
Table 8-11: Change in PROMs from baseline to eight months. Presented as mean (standard deviation) for each group in the RCT, preference group and combined RCT and preference group arms

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=6)</td>
<td>PKT (n=11)</td>
<td>MAT (n=4)</td>
</tr>
<tr>
<td>KOOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>16.12 (7.82)</td>
<td>13.31 (10.24)</td>
<td>33.75 (8.35)</td>
</tr>
<tr>
<td>Pain</td>
<td>28.24 (14.32)</td>
<td>11.36 (17.01)</td>
<td>31.25 (13.10)</td>
</tr>
<tr>
<td>ADL</td>
<td>28.19 (9.68)</td>
<td>6.95 (15.62)</td>
<td>26.47 (18.25)</td>
</tr>
<tr>
<td>Sports</td>
<td>19.17 (19.85)</td>
<td>10.45 (34.17)</td>
<td>26.25 (19.74)</td>
</tr>
<tr>
<td>QoL</td>
<td>26.04 (10.77)</td>
<td>18.75 (10.83)</td>
<td>31.25 (0.00)</td>
</tr>
<tr>
<td>IKDC</td>
<td>11.14 (5.87)</td>
<td>9.92 (13.39)</td>
<td>24.64 (3.44)</td>
</tr>
<tr>
<td>Lysholm</td>
<td>16.00 (16.04)</td>
<td>14.91 (14.49)</td>
<td>26.25 (17.54)</td>
</tr>
</tbody>
</table>

Table 8-12: Change in PROMs from baseline to twelve months. Presented as mean (standard deviation) for each group in the RCT, preference group and combined RCT and preference group arms

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Preference group</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAT (n=5)</td>
<td>PKT (n=11)</td>
<td>MAT (n=4)</td>
</tr>
<tr>
<td>KOOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>21.43 (8.75)</td>
<td>13.31 (15.49)</td>
<td>35.53 (9.32)</td>
</tr>
<tr>
<td>Pain</td>
<td>27.78 (10.39)</td>
<td>11.36 (16.73)</td>
<td>37.50 (12.53)</td>
</tr>
<tr>
<td>ADL</td>
<td>23.82 (10.26)</td>
<td>0.80 (19.77)</td>
<td>24.63 (16.83)</td>
</tr>
<tr>
<td>Sports</td>
<td>20.00 (7.91)</td>
<td>9.09 (30.81)</td>
<td>30.00 (9.13)</td>
</tr>
<tr>
<td>QoL</td>
<td>28.75 (8.39)</td>
<td>19.32 (15.17)</td>
<td>32.19 (11.79)</td>
</tr>
<tr>
<td>KOOS&lt;sub&gt;4&lt;/sub&gt; composite</td>
<td>24.49 (5.31)</td>
<td>13.27 (15.76)</td>
<td>33.81 (4.57)</td>
</tr>
<tr>
<td>IKDC</td>
<td>18.42 (4.37)</td>
<td>7.16 (17.85)</td>
<td>23.71 (7.36)</td>
</tr>
<tr>
<td>Lysholm</td>
<td>22.60 (16.56)</td>
<td>16.46 (17.57)</td>
<td>25.00 (13.95)</td>
</tr>
</tbody>
</table>
A: RCT

B: Preference group
C: Combined RCT and preference group

Figure 8-12: KOOS Symptoms mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups
Figure 8-13: KOOS Pain mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups
A: RCT

B: Preference group
C: Combined RCT and preference group

Figure 8-14: KOOS ADLs mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups

A: RCT
Figure 8-15: KOOS Sports mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups
A: RCT

B. Preference group
C. Combined RCT and preference group

Figure 8-16: KOOS QoL mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups

A. RCT
Figure 8-17: KOOS Composite mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups
A: RCT

B: Preference group
C: Combined RCT and preference group

Figure 8-18: IKDC mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups

A: RCT
Figure 8-19: Lysholm mean and standard deviation change at four, eight and twelve months for A: RCT groups, B: Preference groups and C: Combined RCT and preference groups
Table 8-13: Significance testing for change in PROMs from baseline to twelve months in the RCT arm and combined RCT and preference group arms. A positive mean and confidence interval difference favours surgery.

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>8.12 (-7.97 – 24.20)</td>
<td>0.300</td>
</tr>
<tr>
<td>KOOS Pain</td>
<td>16.42 (-1.16 – 33.99)</td>
<td>0.065</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>23.02 (2.68 – 43.36)</td>
<td>0.029</td>
</tr>
<tr>
<td>KOOS Sports</td>
<td>10.91 (-19.60 – 41.42)</td>
<td>0.456</td>
</tr>
<tr>
<td>KOOS QoL</td>
<td>9.43 (-6.28 – 25.14)</td>
<td>0.219</td>
</tr>
<tr>
<td>KOOS₄ composite</td>
<td>11.22 (-0.21 – 22.65)</td>
<td>0.054</td>
</tr>
<tr>
<td>IKDC</td>
<td>11.26 (-6.39 – 28.92)</td>
<td>0.193</td>
</tr>
<tr>
<td>Lysholm</td>
<td>6.15 (-13.85 – 26.14)</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Table 8-14 shows the pooled standard deviations for the change in PROMs from baseline to twelve months. The KOOS₄ composite pooled standard deviation in the RCT arm was 11.76; the pooled standard deviation was 12.79 in the combined RCT and preference group arms.

Table 8-14: Pooled standard deviations for change in PROMs from baseline to twelve months in the RCT arm and the combined RCT and preference group arms.

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS₄ composite</td>
<td>11.76</td>
<td>12.79</td>
</tr>
<tr>
<td>IKDC</td>
<td>12.99</td>
<td>11.64</td>
</tr>
<tr>
<td>Lysholm</td>
<td>17.07</td>
<td>15.09</td>
</tr>
</tbody>
</table>
8.3.7 Complications

In the meniscal allograft transplantation groups there were three complications in two participants. One participant in the RCT arm had a diagnostic arthroscopy for a suspected meniscal tear at six months. No tear was seen and no other procedure was performed. The second participant was in the preference group and had an arthroscopy within four months of surgery, following a fall, where a haemarthrosis was diagnosed. This was washed out as part of the procedure. Two months later another arthroscopy was performed, where a small tear of the allograft was diagnosed and trimmed.

In the personalised knee therapy group, one participant reported soreness and irritation from the offloading knee brace, requiring it not be used for a period of time.

8.4 Discussion

The aim of a pilot study is to provide information that will inform the design and conduct of a definitive evaluation. This pilot highlighted a number of issues that need careful consideration in the context of a definitive evaluation. One key factor in determining whether a full RCT is deliverable within reasonable timescales is the recruitment rate. In this pilot, twenty-one of the thirty-eight eligible participants consented to be part of the RCT (fifty-five per cent). It is notoriously difficult to recruit into operative versus non-operative RCTs due strong patient preferences, resulting from the wide difference in treatments\(^\text{71}\). One study reviewed publicly funded trials and found it took nearly twice as long to recruit to operative versus
non-operative trials, compared to either operative or non-operative trials. A wide range of recruitment rates have been reported for operative versus non-operative trials: Jarvik et al. reported a recruitment rate of twenty-two per cent in a multi-centre RCT comparing surgical decompression to non-operative treatment for carpal tunnel syndrome. Klazen et al. reported a recruitment rate of forty-two per cent in a multi-centre RCT comparing vertebroplasty to non-operative treatment for osteoporotic vertebral fractures. In a pilot study comparing arthroscopic hip surgery to physiotherapy for the treatment of femoroacetabular impingement (UK FASHIoN), the recruitment rate was seventy per cent. Although a fifty-five per cent recruitment rate is reasonable, it is likely to be higher than what could be achieved if a multi-centre RCT was performed. Lead sites of multi-centre RCTs and single site RCTs are known to recruit at higher rates than satellite centres. The authors of the MRC framework also advise caution when interpreting recruitment and retention rates of pilot studies, as they may not truly reflect a full RCT. It is also possible that the recruitment rate in this pilot RCT was higher because the chief investigator, who is medically trained, recruited all participants. However, previous trials have shown that trained recruiters were able to achieve similar recruitment rates to surgeons, in surgical RCTs. When considering a full RCT, a conservative strategy would be to estimate recruitment time based on a lower recruitment rate than fifty-five per cent.

One strategy to improve recruitment rate could be to expand the eligibility criteria. This may also have the added benefit of increasing the external validity. However, Figure 8-4 shows that no single exclusion criterion accounted for more than four potential participants. It would also not be possible to expand the eligibility criteria
to account for the most common exclusions: Surgeon decision and need for other concurrent surgery.

One of the concerns with studies that have low recruitment rates is the limited external validity. If a very low percentage of eligible participants entered into a RCT, the results of the trial can only be safely applied to future people in clinic that would have been willing to be randomised themselves, which would be unknown. This issue is particularly recognised in operative versus non-operative RCTs, where a comprehensive cohort study design has been suggested\textsuperscript{70,75}. A comprehensive cohort design was used for this study, where patients that were unwilling to be randomised entered preference groups and were followed up in a similar manner. This study design has the advantage of increasing the external validity, but has not been widely used as it has a high cost for a perceived relatively low additional gain\textsuperscript{70}. It has been used successfully where the preference group data provided strong external validity of results of a RCT with a low recruitment rate\textsuperscript{153}. However, it has also failed to be useful when there was a strong preference for one treatment over the other\textsuperscript{148}. In this pilot, there was only a marginal preference for personalised knee therapy (nine participants) compared to meniscal allograft transplantation (six participants), in the preference group arm. It is likely that the recruitment rate for a full RCT will be lower than fifty-five per cent; a comprehensive cohort design may be important to demonstrate external validity in the majority of eligible patients not willing to be randomised. The difficulty with a comprehensive cohort design is whether it is appropriate to merge the outcome data from the randomised and preference groups.
In a pilot, merging the outcomes to get a pooled standard deviation from all participants has the potential advantage of increasing the precision of the estimate of variation in the population, in order to calculate a sample size for a definitive evaluation. This may be particularly useful to assess variation in PROMs in this study where the pilot RCT participant numbers were small, as the sample size was based on the primary outcome measure of MRI volume change. This pilot is also likely to provide an underestimate of the population standard deviation and therefore underestimate the sample size needed in a full RCT. In this light, the potential downsides of merging the RCT and preference groups appear small. In the case of the KOOS₄ composite, the pilot RCT standard deviation was 11.76 and merged standard deviation was 12.79. Using the merged standard deviation in a sample size calculation would be more conservative, requiring a larger sample size.

Merging the outcomes of the RCT and preference groups to increase the power of a study to detect a difference between treatments is more controversial. The main disadvantage of doing this is that you reduce the internal validity of the study by introducing the risk of selection bias. Participants not willing to be randomised are likely to have different characteristics than those that are, risking undermining the whole process of randomisation; for example they may believe one treatment to be far superior to the other. In this study, preference group participants were also treated differently, as they were followed up as per routine follow up appointments, which may also have an effect on the outcomes. Additionally the delay to surgery was less for the preference group participants, which may reflect that some participants had already discussed surgery with the surgeon at previous appointments and progressed
down the surgical route prior to enrolling in the study. This may further change the characteristics of participants in the preference group, compared to the RCT group.

The advantage of merging the groups is that the power of the study to detect a difference is increased. There were no major imbalances in the baseline demographics between the RCT and preference groups. Differences in baseline PROMs were not statistically significant between the meniscal allograft transplantation groups, personalised knee therapy groups or the merged RCT and preference groups, although numbers were too small to draw conclusions with confidence. It was also stated a priori in a published protocol that RCT and preference group results would be merged if appropriate. In this study, the mean difference in the KOOS4 composite score had borderline statistical significance in the RCT (p=0.054), but was statistically significant with merged RCT and preference groups (p=0.001). The IKDC and Lysholm scores were closer to statistical significance in the merged groups, but were not significant at the five per cent level. Whilst the risk of selection bias makes it impossible to draw definitive inferences, these results as they stand, provide evidence that surgical intervention may well benefit patients and that this should be tested in a full RCT. Over interpretation of these results as definitive evidence of effectiveness should be avoided for a number of reasons: The final participants that had a delay to surgery are yet to complete final follow up, which may change the results. The risk of selection bias from combining the RCT and preference groups remains, and the statistical analysis in this study was exploratory in nature. As such, the results may suggest a benefit of one treatment over another, but cannot support inferential conclusions. A fully powered pragmatic multi-centre RCT would be able to do so,
and also has higher external validity to allow a safer extrapolation of the outcome to other centres. Historically, the premature adoption of the results of single centre trials have resulted in ineffective treatments being recommended, or worse, and should be avoided. This pilot showed that there was a long delay to surgery for the majority of participants. The median time to surgery was over six months, even excluding the three participants that did not have surgery within one year of entering the study. This causes two main concerns: Firstly, withdrawing participants from one side of a RCT in this way risks biasing the outcomes. However, the reason for withdrawal was due to the lack of availability of particular sizes of allograft. There is no obvious link between certain sizes of allograft and different outcomes in the general population. Therefore, it was not considered that withdrawing these participants would alter the outcomes, beyond withdrawing any participants at random. Secondly, it poses deliverability of a full RCT issues if thirty per cent of participants assigned to surgery do not receive the intervention within a year and the majority do not receive surgery within six months. It is likely that it would need to be shown that the delay to surgery could be reduced before a definitive evaluation could be undertaken. The delay to finding an allograft is mainly due to waiting for an adequate size match, although administration processes may be streamlined as well. This process could be reduced if more tissue banks were used, giving a larger pool of available allografts. This needs to be weighed against cost and each tissue provider’s credentials, for example whether their sterilisation, storage and administration procedures were considered appropriate.
In this pilot, a recruitment rate of fifty-five per cent equated to 1.75 participants per month. Whilst it is reasonable to assume that this is likely to be relatively constant at UHCW, it is not known how many other centres are performing the operation and how many eligible patients they see monthly. The majority of patients seen for consideration of meniscal allograft transplantation are referred from outside of the local area. It is likely that some other centres are performing considerably fewer meniscal allograft transplantations if they do not get referrals from outside their area. This information would need to be ascertained either before or within an internal pilot for a multi-centre RCT.

Relatively few patients were screened and deemed ineligible for this study (thirteen of fifty-one). This is likely to be due to the set up at UHCW for seeing patients that may be suitable for meniscal allograft transplantation. The operating surgeons screen all referrals and if they are appropriate, requests for further information are sent, including: A completed proforma, radiological and arthroscopic images. Once these steps are completed, patients are seen in once monthly ‘meniscal reconstruction’ clinics. This had two main benefits relating to the study: It reduced the chance of potential participants being missed, and there were fewer inappropriate referrals. This system also explains the almost stepwise recruitment graphs: Clinics were cancelled over Christmas and summer due to a surgeon’s holidays; the extra patients were then seen in proceeding month’s clinic. In considering a full RCT, this set up reduces the number of clinics that researchers need to attend in order to recruit participants at UHCW.
Another key consideration in a full RCT is the choice of primary endpoint. In this pilot, the change in cartilage volume at one year following the intervention was defined as the primary endpoint. No statistically significant differences were seen for cartilage volume change (or any other MRI outcome measure) at twelve months. Whilst it is difficult to draw any conclusions with confidence due to the small sample size, it is interesting to note that the trend in cartilage volume change over time between the two RCT groups was opposite. In the meniscal allograft transplantation group the mean loss is initially higher, which then improved at the eight and twelve month time points. The reverse happened in the personalised knee therapy group, which might be the expected trend in a sample of participants with or at risk of OA. This trend is approximately matched in the cartilage thickness scores. It cannot be known in this study whether this is a true phenomenon or the result of sampling error.

Cartilage volume change represents structural change in the knee and is a surrogate endpoint for the progression of OA. Well validated surrogate endpoints are commonly used in clinical trials, for example blood pressure (as a surrogate for cardiovascular or cerebrovascular disease) and glycosylated haemoglobin (as a surrogate for diabetes)\textsuperscript{145}. The main advantages of using a surrogate endpoint in this pilot are that OA has a long lag time and patients’ symptoms are highly variable. Cartilage volume change can shorten the length of a clinical trial and may also reduce the number of participants needed to determine whether a difference between groups exists\textsuperscript{18}. If, for example, knee replacement was used as an endpoint, an extremely long trial with large numbers of participants would be needed, making it impractical to run. The NICE clinical (national) guideline research recommendations
for OA state that structural changes are more closely linked to OA symptoms than initially thought and that prevention of structural changes is likely to prevent or delay OA\textsuperscript{204}. It is further suggested that appropriate structural endpoints include changes in joint space width on plain radiographs or MRI features of OA. In chapter four it was suggested that joint space width may not be a useful measure in meniscal allograft transplantation trials due to the potential confounding effect of the allograft on joint space width, as well as being insensitive to early OA change. Articular cartilage loss is a cardinal feature of OA and has been increasingly measured, as MRI imaging and interpretation improves\textsuperscript{36, 42, 215}. A number of studies have assessed cartilage changes in the knee using segmented MRI images, similar in technique to the one in this study, finding statistically significant losses at one year\textsuperscript{135, 223, 283}. It has also consistently been shown that the cartilage loss in the central weight bearing region of the tibiofemoral joint is greater than global loss\textsuperscript{90, 135, 161, 223, 283, 288}.

For cartilage volume loss on MRI to be a useful surrogate endpoint, higher losses need to be predictive of future clinically meaningful OA. Knee replacement is recognised as a useful measure of end stage OA, although this also has limitations. It has been shown that higher rates of cartilage loss in the knee are predictive of future knee replacement: Cicuttini et al. studied 113 patients with mild to moderate knee OA, finding an odds ratio of knee replacement at four years of 2.3 for patients with three to eight per cent and 7.1 for greater than eight per cent yearly tibial cartilage volume loss, compared to patients with less than three per cent yearly loss (at two years); they also observed a biological gradient of cartilage loss and risk of knee replacement\textsuperscript{66}. The results of a study by Raynauld et al. showed a stronger association, with an odds ratio of 18.7 for knee replacement at a mean of six years
with greater medial compartment loss and 3.57 for global cartilage loss (at two years), both of which were statistically significant. A recent systematic review on the predictive value of MRI outcomes concluded that cartilage volume loss correlates with joint space loss, is sensitive to change and predicts outcomes in a continuous manner. The authors also stated that it is a useful tool for the evaluation of structural changes and the prediction of knee replacement.

Determining the minimum clinically important difference (MCID) is important in order to calculate a sample size for a definitive RCT. There is no single definitive method for determining the MCID, but there are two general approaches. Using an anchor-based approach has the advantage of being linked to an difference that is clinically meaningful from the patient’s perspective and is often the preferred method. It is however difficult to use this approach for cartilage volume change, as there are no studies that have shown its effect on a clinically meaningful outcome in the patient group under investigation. The nearest comparison may come from the study by Cicuttini et al., where the odds ratio of 7.1 for patients with greater than eight per cent loss compared to those with less than three per cent loss provides a minimum difference of five per cent.

Using this as the MCID and the pooled standard deviation from this pilot of 18.14, a two-sided independent samples t-test with a power of 0.9 and significance level of 0.05, 278 participants are needed in each group for a full RCT. Allowing for a fifteen per cent loss to follow up, 320 are needed in each group (640 in total). However, their results are not directly comparable to the outcome measure used in this pilot as only the central weight bearing area in the affected compartment was assessed. The
effect of this is likely to be that the sample size calculation provides an overestimate
the number of participants needed. Relatively larger cartilage losses were seen in
both treatment groups in this pilot, compared to studies in the literature\textsuperscript{88, 134, 283}. This
may be due to sampling error from the small sample, assessing a focal area of fast
cartilage change, identifying ‘fast-progressor participants’ or a combination of
factors.

An alternative approach is to use a distribution-based method. One advantage of this
approach is that it can account for change beyond some level of random variation\textsuperscript{289}. Several
distribution-based methods have been proposed, with no one method being
definitively determined as superior\textsuperscript{289}. One common method is to define the MCID
as one half of the standard deviation of the change between pre- and post-treatment\textsuperscript{23, 262, 289}. This equates to a standardised effect size of 0.5, which is considered a
‘moderate’ effect\textsuperscript{67, 289}. Using the same power and significance parameters as before,
eighty-five participants are needed in each group for a full RCT. Allowing for a
fifteen per cent loss to follow up, 100 are needed in each group (200 in total).

Whilst there are some advantages to using cartilage volume as the primary endpoint,
there are also some problems with its use. Surrogate endpoints are best when the
pathogenesis of the disease is well understood\textsuperscript{18}. This is not true for OA and
although cartilage loss is a key feature, OA is a heterogeneous and relatively poorly
understood group of diseases, with very few effective disease modifying
treatments\textsuperscript{36}. Whilst there are some encouraging studies showing that higher rates of
cartilage loss are predictive of future OA, there is not a wealth of high level evidence
that can be used to accurately predict a clinically meaningful effect based on a
difference in the rate of cartilage volume loss. These factors limit the validity of cartilage volume as an outcome measure at present. Another key aspect of validating a surrogate endpoint is to demonstrate that a treatment-related change has an impact on the course of the disease; something that has not yet been demonstrated for cartilage change. Surrogates are also situation (or treatment) specific; therefore, the effect of a reduction in the loss of cartilage volume in young patients following meniscal allograft transplantation may not be the same as an older patient with a slow rate of cartilage loss\textsuperscript{145}.

Another limitation of cartilage volume change is the associated measurement error. IMorphics have previously reported their repeatability of cartilage measurement to be around two per cent, using the coefficient of variation (relative standard deviation), which compares well with other studies that have assessed the same thing\textsuperscript{89, 135}. Whilst this is relatively small, it does mean that observed differences may be due, in part, to measurement error. It is not anticipated that measurement error would affect one group more than another, so in a full RCT it is likely that any measurement error would be balanced between groups.

Due to the only partial validation of cartilage volume, its surrogate nature and the difficulties in determining a sample size, it may be more appropriate to use another outcome measure as the primary endpoint. PROMs are gaining increasing popularity as an outcome tool, both in research and in clinical practice, due to an increased acknowledgement that the outcome of treatments should reflect factors that matter to the patient\textsuperscript{199}. PROMs are widely used to assess the treatment response in RCTs with patients that have OA\textsuperscript{86}. Although a large number of PROMs have been used, the
Western Ontario and McMaster Universities Arthritis Index (WOMAC) measure was found to be the most commonly used in OA RCTs\textsuperscript{86}. The KOOS was developed as an extension of the WOMAC measure in the 1990s so that it could be used for younger and more active patients with knee injury that can result in, or has already resulted in OA\textsuperscript{229}. It is intended for short and long term use and has been validated to assess the outcome after a range of knee operations in generally younger patients than the WOMAC measure\textsuperscript{25, 227, 237, 282}. Whilst it has five domains with separate scores, a composite score can be created for use in clinical trials; this was demonstrated in a seminal RCT comparing early ACL reconstruction to potential delayed ACL reconstruction\textsuperscript{107}. The KOOS is used in a number of large databases including the National Institute for Health Osteoarthritis Initiative, a large longitudinal prospective observational study of patients with risk factors for, or established OA\textsuperscript{2}. The KOOS was also unanimously chosen as the primary region specific outcome measure to be used in studies of meniscal allograft transplantation, during a consensus exercise at the most recent International Meniscal Reconstruction Experts Forum meeting (2015) in Lyon, France.

The MCID for the KOOS has not been definitively determined, but a ten point difference has been proposed and also used in previous clinical trials, with a standard deviation of fifteen\textsuperscript{107, 227}. This MCID was determined based on the WOMAC score, where an MCID has been assessed. Whilst a formal assessment of the KOOS would be most appropriate, the KOOS does contain the full version of the WOMAC and is therefore likely to have some similar characteristics. Using these parameters, a two-sided independent samples t-test with a power of 0.9 and significance level of 0.05, forty-eight participants are needed in each group for a full RCT. Allowing for two
groups and a fifteen per cent loss to follow up, 114 participants are needed in total. Using the pooled standard deviation from this pilot RCT of 11.79, thirty participants are needed in each group for a full RCT. Allowing for two groups and a fifteen per cent loss to follow up, seventy participants are needed in total. Using the combined RCT and preference group pooled standard deviation of 12.79, thirty-five participants are needed in each group for a full RCT. Allowing for two groups and a fifteen per cent loss to follow up, eighty-two participants are needed in total. This represents a range of between 70 and 114 participants needed if the KOOS was the primary outcome measure.

The alternative method of defining the MCID as half a standard deviation of the change scores would give a sample of eighty-five participants in each group. Allowing for a fifteen per cent loss to follow up, 100 participants would be needed in each group (200 in total).

The design of a trial depends on the research question being asked. A pragmatic trial is designed to ask whether an intervention works in real life conditions, and is able to answer whether it works, but only gives a limited insight into how it works. An explanatory trial asks whether an intervention works in ideal conditions and is more concerned with how it works, but only gives a limited insight into whether it works in real life conditions. Pragmatic trials have gained increasing popularity in recent years and are more able to drive health policy. These terms represent the ends of a spectrum and a study may contain elements of both designs, depending on the research question.
With a full RCT in mind, the design of this pilot was predominantly pragmatic, with some explanatory components: It had broad eligibility criteria, allowing the surgeon to make an individual judgement as to whether he/she thought a patient would benefit from meniscal allograft transplantation; although patients with significant cartilage loss were excluded, this is representative of the majority of surgeons that report their indications; the intervention and comparator protocols were pragmatic, allowing for variation depending on the individual participant and surgeon/physiotherapist; the interventions themselves were not strictly meniscal allograft transplantation compared to physiotherapy, as osteotomy and bracing were used when malalignment was present. This study design allows an assessment of the full treatment that a patient would receive in real life conditions. One of the limitations of this study design is that the ‘active ingredients’ of the intervention are often difficult to specify\textsuperscript{54, 75, 105}, but this is not a priority for pragmatic trials. Another factor that moves this study towards the pragmatic end of the spectrum is that the interventions were two different treatments that are currently being used on the NHS. This allows the assessment of whether one treatment is superior, regardless of any potential placebo effects\textsuperscript{226}.

The main explanatory components of this study were the choice of primary outcome measure and the decision to define baseline as the start date of the intervention, rather than the day of randomisation. As previously discussed, cartilage volume change is a surrogate endpoint, representing structural progression of OA. A PROM such as the KOOS would be considered a more pragmatic outcome measure as it directly reflects the range of health gains from the patients’ point of view\textsuperscript{226}. When considering a full RCT, a PROM would be a more useful measure to drive the
implementation, or otherwise, of the intervention, whilst cartilage volume change could anchor the results by giving a biological basis for the response to the intervention.

One of the difficulties with the evaluation of meniscal allograft transplantation is that there can be a long delay from the decision to start treatment to the operation. Waiting list delays are not uncommon in elective surgical procedures, which is exacerbated in the case of meniscal allograft transplantation by the need for a size matched graft, as well as the limited number of surgeons that can perform the operation. Waiting list effects can influence outcomes, particularly if the follow up appointments are during the early healing stage after surgery. If, for example, a participant assigned to meniscal allograft transplantation had an eleven month delay to surgery, they would have their final twelve month assessment four weeks following surgery (when the post operative protocol advises non-weight bearing). It is unlikely that the final outcome following surgery would reflect outcome scores at that appointment. The most pragmatic option and most common method is to ‘start the clock’ on the day of randomisation, regardless of waiting list issues. This most closely reflects real life conditions, where waiting list delays could be considered an inadvertent part of the overall treatment. As the primary outcome measure in this pilot was explanatory, it was decided that more useful data would be collected by choosing the start of the intervention as the time to ‘start the clock’ on follow up. It was considered that repeated MRI scans of participants assigned to surgery, but not actually having had surgery would not yield useful data for comparison and would be difficult for participants to understand, potentially resulting in a higher loss to follow up. Whilst there are benefits to this approach when assessing cartilage volume
change, there are some practical and methodological downsides. Participants waiting for meniscal allograft transplantation may well deteriorate, given the progressive nature of OA and perceived lack of treatment. This may result in unbalanced groups at baseline, with a resulting confounding effect on the results. In this study, repeated baseline PROMs in participants waiting over four months for surgery were worse, although these differences were small and not statistically significant. From a practical point of view, the unknown delay to surgery means that the trial endpoint cannot be accurately predicted. In this study, the delay to surgery has resulted in delay to the final results being collected, despite recruiting all participants on time. This may have funding and trial delivery issues for a full RCT.

In a definitive evaluation, if a PROM was the primary outcome measure and the research question was further towards the pragmatic end of the spectrum, it may be more appropriate to start the clock on the day of randomisation. In order to minimise the risk of the primary endpoint conflicting with early post-operative healing, the length of follow up could be increased to two years. The downside of this is that it would have cost, deliverability and loss to follow up issues. A compromise solution may have been found in a recent multi-centre RCT comparing two different types of shoulder surgery and an active monitoring group, for people with shoulder pain. Follow up was collected using the day of randomisation as day zero, but alongside this anyone that waited more than four months for surgery were termed ‘breachers’ and had a further follow up appointment.
8.4.1 Limitations

Meniscal allograft transplantation has been performed for over thirty years and numerous studies have reported their intervention protocols (as shown in chapter three). This allowed for a comparison between the intervention in this study and those used in other centres. The systematic review of physiotherapy in chapter five for this specific patient population revealed very few studies and they were mostly on patients with no or mild pain\textsuperscript{98, 120, 228}. This limits the extent to which comparisons can be made between personalised knee therapy and treatments used in other centres, making it difficult to know how appropriate the intervention might be considered, as well as its external validity. Whilst it may not be possible, or even appropriate, to change an established intervention currently being delivered on the NHS, it is important to know how closely it matches other centres. When comparing it to the physiotherapy treatments used in the studies identified in chapter five, the techniques were similar: There was a focus on strength training as well as core control elements, with a personalised plan for each participant. The one marked difference was that the number of specified treatment sessions was considerably higher in the reported studies. In the study by Roos and Dahlberg there was one initial session then three a week for four months\textsuperscript{228}. In the study by Hall et al. there were eight individual sessions and additional home sessions over twelve weeks\textsuperscript{120}. The personalised knee therapy protocol only specified sessions to be delivered over a minimum of three months. Neither of the studies in the systematic review were delivered on the NHS and it would be unlikely to be feasible to do so. A cross-sectional survey has previously shown that only three per cent of physiotherapists offered greater than seven sessions for patients with knee OA; the majority of physiotherapists offered two or three (forty-one per cent) or four to five (thirty-six per cent) sessions\textsuperscript{130}. The
number of sessions actually received by participants that had personalised knee therapy in this study was similar to that reported in the survey, with twenty-one per cent receiving two to three, thirty-seven per cent receiving four to five and twenty-one per cent receiving six to seven sessions. Although general patients with knee OA are not directly comparable with the young sub-group in this study, it does suggest that the amount of physiotherapy that participants in this study had was similar to what might be realistically achievable on the NHS, given the wide geographical locations of participants and the need to use local physiotherapists.

One potential criticism of the personalised knee therapy protocol is that it might be considered too non-prescriptive to allow the goals to be achieved or the fidelity to be assessed. In 2014, the TIDieR framework was produced which gives guidance on best practice for reporting intervention protocols. Whilst this was published after the intervention protocols in this study were written and therefore was not used, they happened to be mostly reported in accordance with the framework. The main area where the personalised knee therapy protocol differed was that there was not enough detail on the amount, duration and intensity of the physiotherapy required. Whilst the approach taken in this study was not to attempt to alter interventions already being used on the NHS, this has to be balanced against the potential to improve the intervention and the ability to assess it.

The intervention fidelity in this pilot was evaluated with a limited quantitative assessment. Intervention (treatment) fidelity can be defined as the ongoing assessment, monitoring and enhancement of the accuracy and consistency of the intervention to the protocol. It can ensure that the active ingredients of the
intervention are delivered appropriately and consistently. It has been shown that higher intervention fidelity is associated with better outcomes\textsuperscript{85}. However, a full assessment of intervention fidelity is a time consuming and costly process, consisting of an assessment of the intervention providers, delivery of the intervention as well as the understanding and adherence of the participants\textsuperscript{43}. The protocols for both interventions in this study were necessarily pragmatic and personalised to the each participant and local resources. Therefore a full assessment of fidelity would need to use a mixed methods approach, with the gold standard being videotaping or audiotaping of intervention providers and participants\textsuperscript{44}. This would have increased the time and cost, and was not considered a priority for this pilot. It has also been argued that one of the distinguishing features of a pragmatic study, when compared to an explanatory one, is the lack of measurement of fidelity and the absence of special methods to improve it\textsuperscript{258}. This is because pragmatic studies are less concerned with how an intervention works, in comparison to whether it works. It is vital that a pragmatic study replicates a real life setting as much as possible and does not make any attempt to alter this within a trial, if this diverges from clinical practice. If fidelity was low in clinical practice, it would be inappropriate to increase it during a trial and then generalise the results to the clinical setting where fidelity was still low.

Despite the disadvantages of assessing fidelity in a pragmatic study, it can be useful in the interpretation of full trial results, as well as allowing more accurate generalisability to other healthcare settings. If a definitive evaluation was undertaken, a more robust assessment of intervention fidelity should be considered if enough resources could be allocated.
As with fidelity, this study took a purely quantitative approach to assessing outcomes. This limited the amount of useful information that could be gained, when compared to a mixed methods approach. For example, patients unwilling to be randomised could have been asked for their reasons, in order to identify common barriers to entry. However, a mixed methods approach is more time consuming and costly, and the benefits of more information have to be weighed against these downsides.

The orthopaedic group at the University of Warwick have run a number of successful trials at UHCW, including operative versus non-operative trials\textsuperscript{73, 74, 113, 114, 182}. A lot of the processes used in this pilot were similar and all members of the TMG had at least some experience of these trials. Therefore significant problems with the trial delivery were not anticipated and the pilot was set up to ensure this assumption was correct, as well as collecting data on outcome measures. It was considered that if major problems were identified, further feasibility or piloting work could then be undertaken to rectify the issue. This was thought to be more efficient and it is considered a reasonable approach to undergo multiple feasibility or pilot studies before starting a definitive evaluation\textsuperscript{75}. Whilst this approach was taken, it is accepted that a mixed methods approach may have yielded important information that was not achieved in this pilot. It may be useful to consider a mixed methods approach in a definitive evaluation, particularly with regards to recruitment, as the rate achieved in the pilot is likely to be lower in a multi-centre RCT. Barriers to entry could then be fed back to the TMG and appropriate action taken as required.
In this study, RCT participants had MRI scans every four months. When conceiving this study, it was anticipated by experts in the field that cartilage changes on MRI would be detectable by four months. It was also reported in an animal model study comparing meniscal allograft transplantation to meniscectomy that MRI changes could be seen at four months\textsuperscript{150}. Conversely, an observational study analysing cartilage changes in twenty-nine ‘fast progressor’ patients, using very similar image analysis techniques to the ones in this pilot, did not find significant cartilage losses at three or six months\textsuperscript{134}. They concluded that a three month time point is not long enough and that six months may also be too short to detect changes. There has been little evidence to contradict that study and when factoring in the additional time, cost and strain on resources, it might be appropriate to remove the four and eight month scans from the outcome assessment in a full RCT.

## 8.5 Conclusion

There was an improvement in all PROMs in the meniscal allograft transplantation group over personalised knee therapy. These results were statistically significant in all the KOOS sub-domains, except Sports, and composite score in the combined RCT and preference group but not in the RCT group alone. Whilst these results suggest that meniscal allograft transplantation may benefit patients, a full RCT is needed to draw definitive inferences. This study showed that it is possible to recruit and retain participants in a RCT and that on the whole, the trial was delivered as per protocol. There is a significant concern regarding the delay to surgery caused by a combination of lack of availability of grafts and waiting list times, which would need to be optimised before considering a full RCT.
9 Conclusion

9.1 Review of thesis aims and objectives

Despite a traditional reluctance to undertake RCTs in surgery, where their proponents have been described as ‘the fifth horseman of an apocalyptical surgical fundamentalism’\textsuperscript{52}, they have gained increasing popularity in trauma and orthopaedics\textsuperscript{271}. Whilst there is little argument that RCTs are the gold standard study design to test for effectiveness of an intervention, they are expensive and time consuming endeavours\textsuperscript{54}. The development and piloting phases are vital preparatory work, with a failure to perform them potentially resulting in weaker interventions that are less likely to work, harder to evaluate and less likely to be worth implementing\textsuperscript{75}. As well as time and cost implications, there are also ethical implications of performing full RCTs that are unequipped to answer the intended question.

The overall aim of this thesis was to provide the development and pilot work to inform a definitive evaluation of meniscal allograft transplantation in treating patients with a symptomatic meniscal deficient knee, compared to physiotherapy. In order to achieve this, the following specific objectives were set:

- Identify the theoretical basis for why meniscal allograft transplantation may result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.
• Systematically review the current evidence base for whether it does result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.

• Identify the theoretical basis for why physiotherapy may result in a symptomatic improvement and/or reduce or delay the progression of OA in patients with a symptomatic meniscal deficient knee.

• Systematically review the current evidence base for whether physiotherapy does result in a reduction or delayed progression of OA in patients with a meniscal deficient knee.

• Perform a regression analysis of the current series of meniscal allograft transplants at UHCW to determine significant predictors of failure.

• Develop and undertake a comprehensive cohort study incorporating a pilot RCT comparing meniscal allograft transplantation to ‘personalised knee therapy’ in patients with a symptomatic meniscal deficient knee.

• Discuss whether a full RCT would be deliverable, in the light of the results of the findings of this thesis.

In relation to the MRC framework, the first five objectives relate to the development work and the sixth objective relates to the piloting phase. The following chapter discusses the important findings from this thesis and their implications in relation to subsequent phases of the MRC framework.
9.2 Summary of study findings

Following the Introduction in chapter one, chapter two evaluated the theoretical basis, with supporting evidence, for why meniscal allograft transplantation and physiotherapy may be effective interventions.

It was demonstrated that although the structure of the meniscus is still not fully understood, it has a micro- and macrostructure capable of distributing the forces through the tibiofemoral joint. It was also shown that meniscectomy changes the loading pattern, with consequent biochemical and biomechanical changes in the knee. Numerous studies have consistently shown that meniscectomy was a strong predictor of symptomatic OA.

It was shown that meniscal allograft transplantation resulted in a loading pattern that was similar to a knee with a native meniscus, with reduced the peak contact pressures and increased total contact area, compared to a meniscectomised knee. Animal model studies had also shown meniscal allograft transplantation to be chondroprotective.

Physiotherapy has a strong evidence base for improving PROMs in patients with symptomatic OA. It has also been shown that patients had persistent thigh weakness following meniscectomy, which may result in a detrimental effect on both function and progression of OA. Physiotherapy can target this deficit, as well as encourage a return to exercise and sports, which is likely to improve functional outcome and quality of life.
Chapters three and four were systematic reviews, designed to explore the patient reported and radiological outcomes following meniscal allograft transplantation respectively. Chapter three was also designed to identify common practice in order to maximise external validity between meniscal allograft transplantation performed in a trial setting and in reported clinical practice.

The first systematic review identified 1374 meniscal allograft transplantations in thirty-five case series that met the eligibility criteria; there were no RCTs. It found that all used PROMs (most commonly Lysholm, IKDC, Tegner and KOOS) showed a significant increase from baseline to final follow up, although the mean scores were still well below the top score. It was also shown that most studies reported that meniscal allograft transplantation was contraindicated in patients over fifty years of age, in the presence of advanced cartilage damage or severe OA, and that malalignment and ligament instability must be corrected. A recent trend change was from cryopreserved to frozen allografts.

The second systematic review, exploring the radiographic outcomes after meniscal allograft transplantation identified 1056 transplantations across thirty-eight studies that met the eligibility criteria. There were no RCTs and very few comparative studies to assess changes. Pooling the joint space changes across studies, there was a mean loss of 0.032 mm at a mean follow up of 4.5 years. When considering measures of meniscal transplant integrity, meniscal extrusion was an almost universal finding but no clear correlation with clinical scores was reported. Other common MRI findings included: High rates of meniscal healing to the capsule, altered signal intensity and altered meniscal shape compared to the native meniscus.
Chapter five was a systematic review of physiotherapy for the treatment of the meniscal deficient knee. Only two studies were identified that met the eligibility criteria, although these were both RCTs and one study had a second paper that had performed a secondary analysis using MRI data. One study found an improvement in one leg and square hop distances as well as some measures of thigh strength at four months in the physiotherapy group, compared to a no intervention control. On the secondary analysis a significant reduction in cartilage quality on T2 mapping was found in the control group. The second RCT found that difference in peak knee adduction moment between groups was not statistically significant.

Chapter three identified a number of aspects of meniscal allograft transplantation where there was variation in practice across studies. The protocol for meniscal allograft transplantation performed at UHCW was generally in agreement with the majority practice and was not an outlier for any part, with the exception of not having advanced cartilage damage as a contraindication to surgery. Many studies considered that meniscal allograft transplantation would have higher complication rates in the presence of advanced cartilage damage, although others disputed this. Chapter six explored whether advanced cartilage damage was a predictor of failure in the current case series at UHCW using a Cox regression model to balance for other potential predictor variables. It was found that advanced cartilage damage at the time of meniscal allograft transplantation was a strong and statistically significant predictor of failure.
Chapters seven and eight refer to the piloting phase of the MRC framework and detail the protocol and results of a comprehensive cohort study, which incorporated a pilot RCT. The study was able to recruit its target of thirty-six participants within the allotted time of one year, with slightly favourable recruitment to the pilot RCT (twenty-one participants) compared to the preference group (fifteen participants). Three participants were withdrawn from the meniscal allograft transplantation RCT group due to a failure to start the intervention within one year. There were no participants lost to follow up in the RCT arm, although there were two participants in the personalised knee therapy preference group that were lost to follow up. The meniscal allograft transplantation intervention was delivered as per protocol for all participants that received the operation and personalised knee therapy was delivered as per protocol for eighteen of twenty participants. There were no statistically significant differences in any of the MRI measures between the groups at the twelve month time point. All PROMs at twelve months showed a greater improvement in the meniscal allograft transplantation groups compared to personalised knee therapy, which was statistically significant for the KOOS4 composite score and all sub-domains except Sports when the RCT and preference group arms were merged. There were three complications in the meniscal allograft transplantation group (pain requiring an arthroscopy, haemarthrosis and meniscal tear). There was one complication in the personalised knee therapy group (soreness and irritation from an offloading brace).
9.3 Implications and future research

The natural history following meniscectomy is reasonably well understood, with a high proportion of young patients presenting with symptomatic OA of the knee. Whilst efforts have increasingly focussed on preserving the native meniscus, this is not always possible. The need for an effective treatment in this patient population exists but the clinical effectiveness of meniscal allograft transplantation compared to alternative treatments still needs to be definitively determined. The link between meniscal allograft transplantation and reducing the structural progression of OA is even less clear.

This thesis identifies some of the challenges and potential solutions to gaining higher quality evidence to guide best practice in treating patients with a symptomatic meniscal deficient knee. The pilot RCT showed that contrary to initial concerns, the trial was acceptable to a reasonable proportion of patients; both in terms of recruitment and follow up. However, there are some concerns when considering a definitive evaluation. The first relates to the number of centres and total number of meniscal allograft transplantations being performed in the UK. When the thesis was conceived, there was an appetite from a number of centres to get the set up to start performing the surgery. A number of surgeons had visited UHCW for advice on how to achieve this, as well as to learn surgical techniques. Since then, it is not clear how many surgeons were successful but it is known that some were not able to set up a service due to local funding and logistical reasons. At the recent International Meniscal Reconstruction Experts Forum meeting in Lyon, there were four UK surgeons identified as regularly performing the operation. It is thought that four or five others may also be performing the operation regularly. The first step would be to
identify the centres in which meniscal allograft transplantation is performed, the number they do each year and the indications they use. The centres in which meniscal allograft transplantation is performed could potentially be identified from tissue banks that provide the allografts, amongst other means.

The second concern is the delay to surgery in the pilot study. There was an over six month delay for eight of the ten randomised participants, of which three were withdrawn after a year of waiting for the intervention. This poses issues to the trial design and there would need to be evidence that this had improved before starting a full RCT.

However, despite the challenges of performing a definitive evaluation of meniscal allograft transplantation compared to physiotherapy identified in this thesis, a full trial is, in principle, warranted and deliverable.
Appendices

Appendix A: Protocol for ‘Meniscal allograft transplantation in a symptomatic deficient knee systematic review’; published on the PROSPERO register of systematic reviews1.

PROSPERO International prospective register of systematic reviews

Meniscal allograft transplantation in a symptomatic meniscal deficient knee: a systematic review

Nick Smith, Matthew Costa, Nicola MacKay, Tim Spalding

Citation

Review question(s)
The primary objective is to assess the clinical outcome following meniscal allograft transplantation (MAT) using any patient reported outcome measure.

The secondary objective is to provide a review of the complications and failures, indications, graft type, operative technique, associated procedures, rehabilitation, radiological findings and graft healing.

Searches
Medline, Embase and the Cochrane library will be searched for published studies.

The World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and Clinical Trials Registry (http://clinicaltrials.gov) will be searched for ongoing or completed trials. The ‘Web of Science’ (http://thomsonreuters.com/web-of-science/) will be searched for conference proceedings.

Restrictions will be for 'humans' and 'English language'.

Types of study to be included
Inclusion:
All clinical comparative studies (including randomised controlled trials) and case series.

Exclusion:
Case reports.

Condition or domain being studied
Patients with a meniscal deficient compartment of the knee and with associated symptoms. Symptoms may include pain, swelling and/or stiffness.

Participants/ population
Inclusion:
Any human of any age.

Intervention(s), exposure(s)
Inclusion:
Meniscal allograft transplantation by any surgical technique and any graft type may be used.

Any rehabilitation regime.

Exclusion:
Non-allografts, for example synthetic meniscal scaffolds.

**Comparator(s)/ control**
If a comparative study, the comparator should be a matched control group or a reasonable alternative to meniscal allograft transplantation, such as physiotherapy, or placebo.

**Outcome(s)**
- **Primary outcomes**
- **Inclusion:**
  Studies must include a patient reported outcome measure. It is expected that the Lysholm, IKDC and Tegner questionnaires will be most commonly used, but any other PROM used will qualify for inclusion.
  - A minimum of 1 year follow-up following surgery.

- **Secondary outcomes**
  - Failures and complications, radiological findings such as osteoarthritis progression, graft healing.

**Data extraction, (selection and coding)**
Two researchers will review the results of the searches independently (NS and NM). Differences will be resolved by discussion and then senior review by MC if differences are not resolved.

**Risk of bias (quality) assessment**
Studies will be assessed for risk of bias.

**Missing studies**
Trials registries will be searched. If a trial has been registered (and completed) but not published, attempts will be made to find the results.

**Missing information and outcomes**
Evidence of missing information and outcomes will be gathered from reviewing protocols (if available) and comparing the methods (numbers entered the study) with the results (numbers analysed).

For failures and complications, if there is no evidence of reporting then these studies will be excluded from the data synthesis.

**Strategy for data synthesis**
The majority of the systematic review will be qualitative. Weighted means will be used to give average Lysholm, IKDC and Tegner scores pre-operatively and at final follow up. Weighted means will also be used to calculate average age at the time of surgery, failure and complication rate.

**Analysis of subgroups or subsets**
None.

**Contact details for further information**
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Organisational affiliation of the review
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Professor Matthew Costa, University of Warwick
Ms Nicola MacKay, None
Mr Tim Spalding, University Hospitals Coventry and Warwickshire

Anticipated or actual start date
10 March 2014

Anticipated completion date
25 April 2014

Funding sources/sponsors
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Conflicts of interest
None known

Language
English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Menisci, Tibial; Transplantation, Homologous

Stage of review
Ongoing

Date of registration in PROSPERO
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Date of publication of this revision
28 March 2014

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**PROSPERO International prospective register of systematic reviews**

**Does meniscal allograft transplantation protect the knee from osteoarthritis? A systematic review**

*Nick Smith, Ben Parkinson, Charles Hutchinson, Matthew Costa, Tim Spalding*

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**Citation**


**Review question(s)**

Does meniscal allograft transplantation reduce or delay the progression of osteoarthritis in patients with a symptomatic meniscal deficient compartment of the knee?

Does the meniscus allograft have a similar appearance to a native meniscus, using magnetic resonance imaging as the outcome tool?

**Searches**

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched. The search strategy will be sensitivity maximising.

Restrictions of studies involving Humans, and also written in the English language will be used.

**Types of study to be included**

Any clinical study (randomised controlled trial, non-randomised comparative study or case series) written in the English language. Studies that do not contain new patient data, biomechanical studies, and case reports will be excluded.

**Condition or domain being studied**

Patients with a symptomatic, meniscal deficient compartment of the knee. Most commonly patients have a history of previous meniscectomy from a sport related injury, but all patients with knee symptoms and have a meniscal deficiency will be included.

**Participants/ population**

Any human of any age.

**Intervention(s), exposure(s)**

Meniscal allograft transplantation using any allograft preserving method and any grafting technique.

Any rehabilitation regime post-operatively.

**Comparator(s)/ control**

If a comparator group exists, it should be a reasonable alternative treatment, for example a non-operative rehabilitation group. It would also be considered reasonable to use the participants' other knees as a comparator.

**Outcome(s)**

Primary outcomes

Change in any radiological OA progression measure.

A minimum of one year post intervention.
Secondary outcomes
Magnetic resonance imaging measures of the meniscus, including: meniscal appearance, signal intensity, healing and extrusion.

A minimum of 6 months post intervention.

Data extraction, (selection and coding)
Results of the database searches will be transferred into EndNote and duplicates will be discarded. Our eligibility criteria will be used to assess the remaining studies using the title and abstract. The full papers of any remaining studies will then be reviewed. Two reviewers (NS and BP) will independently assess studies for eligibility. Any discrepancies will be resolved by discussion and if that fails, by the judgement of a senior author (TS).

In order to reduce duplicate publication bias, if two or more eligible studies used some or all of the same participants, both studies will only be included if different outcomes measures are used. Only the study with the longest follow up will be included if the same outcome measure is used.

Risk of bias (quality) assessment
A qualitative risk of bias assessment will be undertaken, using Cochrane guidelines. The risk and effect of missing studies and missing outcomes will be assessed.

Strategy for data synthesis
No formal meta analysis will be performed. Weighted means will be used for joint space width changes and meniscal extrusion.

Analysis of subgroups or subsets
None planned.

Dissemination plans
It is anticipated that we will publish the systematic review in a peer reviewed orthopaedic journal.

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Mr Tim Spalding, University Hospitals Coventry and Warwickshire

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Conflicts of interest
None known

Language
English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Knee Joint; Osteoarthritis; Transplantation, Homologous

Stage of review
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PROSPERO
International prospective register of systematic reviews
The information in this record has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.
Appendix C: Protocol for ‘Physiotherapy for a patient with a post-meniscectomy knee systematic review’; published on the PROSPERO register of systematic reviews.

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Physiotherapy for patients with a symptomatic meniscal deficient knee: a systematic review

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
25/03/2015

4 Anticipated completion date
Give the date by which the review is expected to be completed.
28/05/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Piloting of the study selection process</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Formal screening of search results against eligibility criteria</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Data extraction</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Risk of bias (quality) assessment</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Data analysis</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Dr Smith

7 Named contact email
Enter the electronic mail address of the named contact.
nickasmith@doctors.net.uk

8 Named contact address
Enter the full postal address for the named contact.
CSRL University of Warwick Clifford Bridge Road Coventry CV2 2DX

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
+44 (0)7825185953

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

<table>
<thead>
<tr>
<th>Title</th>
<th>First name</th>
<th>Last name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Dr</td>
<td>Nick</td>
<td>Smith</td>
<td>University of Warwick</td>
</tr>
<tr>
<td>Mr</td>
<td>David</td>
<td>Wright</td>
<td>UHCW</td>
</tr>
<tr>
<td>Professor</td>
<td>Matt</td>
<td>Costa</td>
<td>University of Warwick</td>
</tr>
<tr>
<td>Mr</td>
<td>Tim</td>
<td>Spalding</td>
<td>UHCW</td>
</tr>
</tbody>
</table>

Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Arthritis Research UK (grant number 20149)

Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Review methods
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
The primary objective is to assess the outcome of patients with a symptomatic meniscal deficient (compartment of the) knee after any physiotherapy intervention, using any patient reported outcome measure.

Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment. MEDLINE, EMBASE, CHNAHL and the Cochrane library will be searched for published studies. The World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and Clinical Trials Registry (http://clinicaltrials.gov) will be searched for ongoing or completed trials. The ‘Web of Science’ (http://thomsonreuters.com/web-of-science/) will be searched for conference proceedings. Restrictions will be for 'humans' and 'English language'.

URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Patients with a meniscal deficient compartment of the knee and with associated symptoms. Symptoms may include pain, swelling and/or stiffness.

Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Any human of any age.
### Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed. 
Inclusion: Any exercise-based therapy intervention delivered over any time period. Exclusion: Non-exercise-based therapies, for example acupuncture, patient education.

### Comparator(s)/control
Where relevant, provide details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). If a comparator exists, any reasonable alternative to physiotherapy would be appropriate.

### Types of study to be included initially
Provide details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated. 
Inclusion: All clinical comparative studies (including randomised controlled trials) and case series. Exclusion: Case reports.

### Context
Provide summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

### Primary outcome(s)
Provide the most important outcomes. Studies must include a patient-reported outcome measure. Ideally, a validated and disease or joint specific outcome measure would be used, but any patient-reported outcome measure would qualify for inclusion. There is no minimum time at which outcomes may be reported. 
Give information on timing and effect measures, as appropriate.

### Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None. 
Health professional reported outcome measures such as muscle strength, will be reported and radiological outcome measures will also be reported; particularly assessing any chondroprotective effects. 
Give information on timing and effect measures, as appropriate.

### Data extraction, (selection and coding)
Provide the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted. 
Two researchers will review the results of the searches independently (NS and DW). Differences will be resolved by discussion and then senior review by MC if differences are not resolved.

### Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis. 
Studies will be assessed for risk of bias. Missing studies: Trials registries will be searched. If a trial has been registered (and completed) but not published, attempts will be made to find the results. Missing information and outcomes: Evidence of missing information and outcomes will be gathered from reviewing protocols (if available) and comparing the methods (numbers entered the study) with the results (numbers analysed).

### Strategy for data synthesis
Provide the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given. 
The majority of the systematic review will be qualitative. Weighted means will be used to give average outcome measure scores if multiple studies have used the same outcome measure.

### Analysis of subgroups or subsets
Provide any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned. 
None.

### Review general information

### Type of review
Select the type of review from the drop down list.
Intervention

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
   English
   Will a summary/abstract be made available in English?
   Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multinational collaborations select all the countries involved. Use the control key to select more than one country.
   England

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
   Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
   We intend to publish this review in a peer reviewed journal on completion.
   Do you intend to publish the review on completion?
   Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
   physiotherapy
   meniscal deficiency
   knee
   patient reported outcomes

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
   Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.
Appendix D: Technique paper for Meniscal allograft transplantation, as performed at UHCW NHS Trust. Currently in press at the time of submission of this thesis.

Technical Note

Arthroscopic Meniscal Allograft Transplantation With Soft-Tissue Fixation Through Bone Tunnels

Tim Spalding, F.R.C.S.(Orth), Ben Parkinson, P.R.A.C.S.Orth, Nick A. Smith, M.Sc., M.R.C.S., and Peter Verdonk, Ph.D.

Abstract: Meniscal allograft transplantation improves clinical outcomes for patients with symptomatic meniscus-deficient knees. We describe an established arthroscopic technique for meniscal allograft transplantation without the need for bone fixation of the meniscal horns. After preparation of the meniscal bed, the meniscus is parachuted into the knee through a silicone cannula and the meniscal horns are fixed with sutures through bone tunnels. The body of the meniscus is then fixed with a combination of all-inside and inside-out sutures. This technique is reliable and reproducible and has clinical outcomes comparable with those of bone plug fixation techniques.

The menisci of the knee act as load distributors as well as secondary stabilizers of the knee. Meniscal allograft transplantation is indicated for patients with a symptomatic meniscus-deficient compartment of the knee. Arthroscopic meniscal allograft transplantation with soft-tissue fixation is a less complicated and more minimally invasive procedure than bone plug techniques while still obtaining stable and secure graft fixation.

Technique

Our technique has been broken down into 10 key stages under the subheadings in this section and is shown in Video 1. The key messages of this technique are summarized in Table 1.

Patient Positioning

The procedure is performed with the patient under general or regional anesthesia with appropriate prophylactic antibiotics. The patient is positioned supine on the operating table with a thigh tourniquet, a single-thigh side support, and a footrest supporting the knee at 90°. For a lateral meniscal transplant, the knee will be moved to the figure-of-4 position. For a medial meniscal transplant, the leg will be abducted and rest against the outer hip of the operating surgeon.

Graft Preparation

The meniscal allografts are sourced from either NHS Blood and Transplant Tissue Services (Liverpool, England) or JRF Ortho (Centennial, Colorado) (imported by Fannin, Dublin, Ireland). The allograft is thawed to room temperature per the tissue bank’s specific instructions (usually about 15 minutes in warm water or 1 hour at room temperature). The graft is dissected from the tibia, trimmed to its true margin, and freshened by the assistant at the start of surgery. The superior surface of the meniscus is marked to aid in orientation (Fig 1). In the case of the lateral meniscus, the most anterior margin of the popliteal hiatus is also marked and a No. 2 nonabsorbable suture is placed as an oblique vertical mattress suture. For the medial meniscus, a similar vertical mattress suture is inserted at a point at 40% of the circumference from posterior to anterior. This represents the middle traction suture (Fig 2A). No. 2 Ultrabraid sutures (Smith & Nephew, Andover, MA) are placed into the posterior and anterior horns using a modified whipstitch, with passage of the suture a minimum of 3 times along the meniscus and back again to ensure a good hold. It is important to ensure that the sutures emerge on the inferior aspect of the footprint of the meniscal horn. The prepared graft
Table 1. Key Messages for Performing Meniscal Allograft Transplantation With All-Suture Technique

<table>
<thead>
<tr>
<th>Message</th>
</tr>
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<tbody>
<tr>
<td>This technique allows insertion of the meniscal allograft without bone</td>
</tr>
<tr>
<td>plugs</td>
</tr>
<tr>
<td>Secure fixation of the meniscal horn is achieved through bone tunnels</td>
</tr>
<tr>
<td>at the attachment sites</td>
</tr>
<tr>
<td>Peripheral fixation is achieved using a combination of inside-out</td>
</tr>
<tr>
<td>and outside-in suture systems</td>
</tr>
<tr>
<td>This technique has several advantages over using bone blocks, with</td>
</tr>
<tr>
<td>comparable results</td>
</tr>
</tbody>
</table>

(Fig 1) is then wrapped in a vancomycin-soaked swab (500 mg in 100 mL of saline solution) and placed securely on the scrub table, awaiting implantation.

Knee Arthroscopic Evaluation

The thigh tourniquet is inflated, and longitudinal (anteromedial and anterolateral) arthroscopy portals are made to allow for later extension. The treatment of the chondral lesions in the affected compartment, noting that the optimal indication for transplantation is chondral surfaces showing changes of International Cartilage Repair Society grade 3a or less.

Recipient Bed Preparation

The host meniscus is assessed and prepared by resecting the remaining meniscal tissue using a combination of arthroscopic punches and a shaver to leave, where possible, a 1- to 2-mm peripheral vascular rim of native meniscal tissue that will support the meniscal allograft. The recipient bed and synovium are rasped using a diamond-tipped rasp and fenestrated with a microfracture awl to stimulate healing and vascularization of the graft.

![Image](Fig 1. The meniscal allograft has been dissected from the tibia and trimmed. It has then been labeled to aid orientation when inserting the graft into the knee. Whisker-like fibers have been placed on the anterior and posterior horns to aid insertion and securing of the graft roots to the knee.)

Posterior and Anterior Horn Insertion-Site Preparation

The tunnel positions for the meniscal horn attachment points are summarized in Table 2. The meniscal horn insertion sites are prepared using a combination of an angled punch to resect the remaining meniscus, a meniscal shaver, and a closed-end curette, with exposure of subchondral bone over a 5- to 6-mm diameter area.

Posterior and Anterior Horn Tunnel Creation

To prepare for the bone tunnels of the meniscal horn sutures, a 2-cm horizontal skin incision is made on the proximal tibia (opposite side to the transplanted meniscus). On the medial side, this is just above the hamstrings tendon insertion on the bare area of the tibia, and on the lateral side, this is just under the flare of the anterolateral tibia. A 1-cm area of bare bone is exposed, elevating the tissue and periosteum. A contralateral working portal to the affected compartment is created by extending the relevant longitudinal arthroscopy portal to 2 cm, followed by insertion of a silicone cannula (PassPort; Arthrex, Naples, FL) (Fig 2A).

A meniscal allograft transplantation drill aiming guide (Smith & Nephew) is inserted through the working portal and positioned in the posterior horn insertion point. The drill guide sleeve is then inserted into the handle and positioned onto the tibia through the prepared incision. The posterior horn suture tunnel is drilled with a long 2.4-mm diameter Beach pin, with visualization of the tip emerging through the bone. The guidewire is overdreilled with a 4.5-mm cannulated Endobutton drill (Smith & Nephew), with the tip left carefully positioned just proud in relation to the tibial plateau surface. A closed-end curette can be used to help protect against inadvertent damage to the articular surfaces and to help retract meniscal tissue, aiding visualization. The guidewire is removed, leaving the Endobutton drill bit in situ. A loop of No. 2-0 Prolene (Ethicon, Somerville, NJ) is passed through the 4.5-mm Endobutton drill bit on a suture passer and is retrieved through the working portal using a suture manipulator (Fig 2B). The free end of this lead suture is passed through the loop and clipped so that it hangs unsupported out of the way.

The meniscal transplantation drill aiming guide is reintroduced through the working portal. The tunnel for the anterior horn is drilled in the center of the attachment footprint with the same sequence of steps. The suture ends are brought out through the working portal, clipped, and hung to the opposite side of the knee (Fig 2A). The suture manipulator is run along the sutures to ensure that there is no twisting or soft-tissue catching.

Middle Traction Suture

An 18-gauge needle is used to localize the correct insertion point. For the lateral meniscus, this point is
Fig 2. (A) The lead sutures have been passed through the bone tunnels and out through the working portal. The middle traction suture has also been passed just anterior to the popliteus tendon and out through the working portal. The Arthrex PassPort silicone cannula is inserted through the working portal. (B) A lead suture is passed through the previously drilled posterior horn tunnel. This is then pulled through the working portal with a suture manipulator and clipped to the side. The same technique is used for the anterior horn tunnel.

just anterior to the popliteus tendon. For the medial meniscus, it is at 40% of the meniscal circumference from the posterior horn insertion. An Accupass suture device (Smith & Nephew) preloaded with a loop of No. 1 PDS (Ethicon) is then used, from outside in, to position 2 loops of sutures on the superior and inferior aspects of the meniscal bed directly above each other. Each loop is then gathered through the working portal and clipped to one side, with the surgeon once again checking for twisting with the other suture loops.

**Graft Passage**

The graft is “parachuted” through the working portal into the knee joint. The assistant holds the graft in the correct orientation adjacent to the working portal (Fig 3). Starting with the posterior horn sutures and then working anteriorly, all the meniscal sutures are pulled into position using the pre-placed shuttle sutures. The graft is now ready to be delivered into the knee through the working portal. Traction is first applied through the posterior sutures to pull the meniscus into the knee. The middle traction sutures are then used to complete the insertion of the meniscus into the knee. There is no traction applied to the anterior horn sutures until the meniscus is in place within the knee.

The anterior and posterior horn sutures are held temporarily over the bone bridge using a single knot throw and a clip. The graft is inspected arthroscopically to assess graft size and position, ensuring that it is snug against the meniscal bed.

**Graft Fixation**

The graft is fixed using a hybrid technique of all-inside, inside-out, and outside-in suture systems. With the arthroscope initially in the working portal, the first Fast-Fix 360 Meniscal Repair device (Smith & Nephew)

### Table 2. Optimal Meniscal Horn Insertion Points for Medial and Lateral Meniscal Horns

<table>
<thead>
<tr>
<th>Meniscal Location</th>
<th>Optimal Horn Insertion Point</th>
</tr>
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<tbody>
<tr>
<td>Medial meniscus</td>
<td></td>
</tr>
<tr>
<td>Posterior horn</td>
<td>Just posterior to medial tibial spine</td>
</tr>
<tr>
<td>Anterior horn</td>
<td>Anterior and medial to insertion of ACL on superior surface of tibial plateau</td>
</tr>
<tr>
<td>Lateral meniscus</td>
<td></td>
</tr>
<tr>
<td>Posterior horn</td>
<td>Just posterior to ACL between tibial spines</td>
</tr>
<tr>
<td>Anterior horn</td>
<td>Anterior to lateral tibial spine and just lateral to ACL</td>
</tr>
</tbody>
</table>

ACL, anterior cruciate ligament.

Fig 3. The meniscal horn whipstitches have been passed through the working portal and out through the bone tunnels. The allograft is then pulled into the knee using the whipstitches and middle traction suture. The posterior horn is the lead suture for pulling the allograft into the knee.
is introduced through the ipsilateral compartment portal using a slotted cannula. With tension being held on the middle sutures, the posterior third is fixed to the prepared meniscal rim using the Fast-Rix 360 system, inserting sutures on the superior and inferior surfaces in a stacked vertical mattress pattern. Portals can be switched to ensure that an adequate fixation angle is achieved. A minimum of 4 suture devices are recommended, and by Joysticking with the needle, the allograft can be optimally placed on the rim.

The middle and anterior thirds of the meniscal graft are secured using an inside-out suture technique with No. 2-0 Ultrabraid. The sutures are inserted from the working portal in a stacked vertical mattress pattern (Fig. 4A and B). A curved inside-out cannula system is used, preferably achieving at least 6 to 8 loops in the body and anterior third, evenly spread on the superior and inferior surfaces of the meniscus. If there is inadequate suture hold on the anterior 1 to 2 cm, then an outside-in technique should be used.

**Final Suture Fixation**

When the sutures are being tied, it is important to evaluate the position of the meniscus in the knee. The sutures should be tied so that the meniscus fits snugly against the capsule (Fig. 4C). In general, the capsule sutures are tied first, and the order is determined by visual assessment of the meniscus. Finally, the anterior and posterior horn sutures are tied under strong tension over the bone bridge, thereby minimizing radial displacement and extrusion.

**Discussion**

Meniscal allograft transplantation has been performed for over 30 years and has consistently been shown to improve clinical outcomes.\(^1\)\(^-\)\(^3\) It may also reduce the

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**Fig 4.** (A) The lateral meniscal allograft is in place (left knee), and vertical mattress sutures are placed at its superior surface. (B) The lateral meniscal allograft is in place (left knee), and vertical mattress sutures are placed at its inferior surface. (C) Final position of the lateral meniscal allograft transplant in the left knee. The meniscal horn sutures have been tied over the bone bridge, and sutures to the body have also been tied.
known high risk of osteoarthritis in these patients, although high-quality evidence for this is lacking. The 2 most common types of meniscal horn fixation are soft-tissue fixation (described in this report) and bone fixation. Recent studies have failed to show a significant biomechanical or clinical advantage of bone plug fixation over an all-suture technique. Meniscal transplants secured by soft-tissue fixation have shown histologic advantages compared with bone plug fixation grafts. Significantly higher cellular viability and collagen organization were found on biopsy of the grafts secured by soft-tissue fixation only, which may be related to a higher immunologic host response caused by the addition of bone plugs. There is also a risk of increased articular cartilage damage if the bone plugs are malpositioned. A meta-analysis and clinical studies have shown comparable outcomes between the 2 different fixation techniques. Although both techniques are viable options for meniscal allograft fixation, the technique described in this report provides a reliable method for surgeons to undertake meniscal transplantation.

References
Appendix E: Research Ethic Committee favourable ethical decision letter.

03 October 2013

Mr Nicholas Smith
Clinical Research Fellow
University of Warwick
Clinical Sciences Research Laboratories
Clifford Bridge Road
Coventry
CV2 2DX

Dear Mr Smith

Study title: A Comprehensive Cohort Study of Meniscal Allograft Transplantation versus Personalised Knee Therapy for Patients with a Symptomatic Meniscus Deficient Knee.

REC reference: 13/WM/0315
IRAS project ID: 125446

Thank you for your letter which was received 02 October 2013, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Wendy Rees, NRESCommittee.WestMidlands-solihull@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management
Appendix F: Local Research and Development ethical approval letter.

22 November 2013

Mr Nicholas Smith
Clinical Research Fellow
University of Warwick
Clinical Sciences Research Laboratories
Clifford Bridge Road
Coventry
CV2 2DX

Dear Mr Smith

Study Title: A Comprehensive Cohort Study of Meniscal Allograft Transplantation versus Personalised Knee Therapy for Patients with a Symptomatic Meniscus Deficient Knee

Thank you for submitting the above study for consideration by the Research & Development Office. I am pleased to inform you that your study has been approved.

To meet national recruitment targets, you need to ensure that you recruit the first patient into this study by 22nd December 2013. Please contact the R&D team if you need support in order to achieve this target.

Approved documents
The documents approved for use in this study are:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
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<td>17/07/2013</td>
</tr>
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<td>01/09/2013</td>
</tr>
<tr>
<td>Participant Information Sheet: Follow-up Only</td>
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<td>17/07/2013</td>
</tr>
<tr>
<td>Participant Consent Form</td>
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<td>17/07/2013</td>
</tr>
<tr>
<td>Participant Consent Form: Follow-up Only</td>
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<td>17/07/2013</td>
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<tr>
<td>GP Letter</td>
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<td>17/07/2013</td>
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<td>Questionnaire: EQ 5D Quality of Life</td>
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</table>
Appendix G: Participant Information Sheets for the MeTEOR pilot study.

Clinical trial of meniscal transplantation compared to personalised knee therapy

Chief Investigator: Mr Nicholas Smith

Participant information sheet

We would like to invite you to take part in a research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have.

Contacts for further information
If, at any time, you would like further information about this research project you may contact the chief investigator Nicholas Smith on telephone number 02476968622. For independent advice contact the PALS service (Patient Advice Liaison Service) at freephone 0800 0284203.

Background information
The meniscus is an important structure within the knee joint. One of its key roles is to cushion impact and protect the gliding surface of the joint from wear. Patients that have damaged their meniscus resulting in removal of the majority of the meniscus (near total meniscectomy) are more likely to develop arthritis in the knee due to this wear of the joint surface.

At present, there are several treatment options for a damaged meniscus ranging from knee therapy to a replacement meniscus also known as a ‘meniscal transplant’.

What is the purpose of this study?
Meniscal transplant is thought to provide cushioning to the joint surfaces and improve symptoms but it has a long recovery period and the operation carries risks of surgery as well as not helping with symptoms. At present there is no direct evidence that meniscal transplant is better or worse than a specific targeted rehabilitation and therapy program.
In this study, we will compare two treatments for patients with an injury to the meniscus and near total meniscectomy. One group of patients will have a course of personalised knee therapy and the other group will have a meniscal transplant.

After the treatment, we will use scans of the knee to carefully monitor the surface of the knee joint to check for damage. The scans are magnetic resonance imaging (MRI) scans.

Both of these treatments are already used within the NHS. However, it is important to perform studies that compare one type of treatment to another so that we can offer the best possible treatment in the future.

**What is a MRI scan and are there any side effects?**
The Magnetic Resonance Imaging (MRI) scanner uses magnetic and radio waves and it does not involve any exposure to x-rays or any other ionizing radiation. The MRI scans will produce a detailed picture of your knee surface cartilage. MRI scans have been used for approximately 30 years and are considered very safe. There are no known side effects associated with a MRI scan, although a small number of people may suffer from claustrophobia (a fear of confined spaces). If this happens, the scan will be stopped immediately. The scan does not hurt and you cannot feel it.

**Why have I been chosen?**
You have been chosen because you have damage to your meniscus and are now having symptoms in your knee due to removal of the majority of the meniscus such that you would be a candidate for meniscal transplant surgery. All patients like you will be invited to take part in this study.

**Do I have to take part?**
It is up to you whether you take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of your care.

**Which treatment will I get?**
If you agree to take part, you will be allocated to either the meniscal transplant group or the personalised knee therapy group. The allocation process will be done by a computer and will be done purely by chance. To answer the question set out in the purpose of the study, we will compare the results we get from one treatment group with the results from the other.

**What will happen after I have been placed in one of the two groups?**
If you are allocated to the meniscal transplant group, we will book you for meniscal transplant surgery. Before the surgery, you may have a course of physiotherapy and a brace if required.

The operation itself is through keyhole surgery. Your new meniscus is from a donor and is inserted into the knee through a small cut at the front of the knee. It is held in position by strong stitches that are placed using the keyhole technique. Your small
wounds will then be stitched and you will have a bandage placed on the knee. After surgery, you will be given crutches to walk and will have a course of physiotherapy. You will be able to put all your weight on your leg at eight weeks after surgery.

If you are allocated to the personalised knee therapy group, you will receive a knee therapy course that has been specifically designed to treat patients like yourself. Each therapy course is unique, depending on the individual patient’s needs and will be designed by a senior physiotherapist. The course will focus on the symptoms of pain and swelling of the knee and will attempt to improve strength and range of movement. The course will focus on the knee joint but will also address the hip, ankle and walking pattern as these can affect your knee. The course will be delivered over at least a three month period, which can be extended depending on your needs.

For both groups, we will arrange a scan before your treatment and at four, eight and twelve months after your treatment. On the days of your scans you will be seen in clinic as usual and be given a set of questionnaires to fill in to assess your progress. The questionnaires will ask about your knee function as well as your general well being. The flow diagram below shows what will happen if you choose to enter the trial.

What are the possible disadvantages and risks of taking part?
There are risks with meniscal transplant surgery, including surgical risks of tearing the new meniscus, persistent knee pain, infection and blood clots, but these are the same risks as for patients that do not take part in the study. The risks associated with personalised knee therapy are also the same for patients that do not take part in the study. There are no other special risks over and above what your doctor would normally inform you about.

**What are the possible benefits of taking part?**
There are no specific benefits of taking part in this research. However, this study may help future patients decide about the best treatment for them.

**What if new information becomes available?**
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your consultant will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your surgeon will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your surgeon might consider it to be in your best interest to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

**What happens when the study ends?**
You will be in the study for twelve months following your operation. If you are still having problems after this time, we will arrange for you to have an appointment with an appropriate specialist to continue your care.

**What if something goes wrong?**
In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against the UHCW NHS Trust (Mrs Ceri Jones, R&D services manager, 0247696196) or University of Warwick (Miss Nicola Owen, Deputy Registrar, 02476522713), but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my taking part in this study be kept confidential?**
All the information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your GP and other doctors who may treat you, but are not part of this study will be notified that you are taking part in this study.

**What will happen to the results of the research study?**
This study is expected to last two and a half years. At the end of the study we will publish the findings in medical journals and at medical conferences. You will not be identified in any reports or publications resulting from the study. If you would like to obtain a copy of the published results, please ask your doctor.
What will happen if I decide not to participate in the research study?
If you decide not to participate in the research study you will continue to be treated by your doctor with the same care as any other patient with your symptoms.

Who has reviewed this study?
This study has been reviewed and approved by Solihull Research Ethics Committee.

Clinical trial of meniscal transplantation compared to personalised knee therapy

Chief Investigator: Mr Nicholas Smith

Participant information sheet – follow-up only

As part of our research we would also like to collect information from patients that do not wish to take part in the clinical trial. This information sheet will explain the information that we would like to collect. One of our team will go through it with you and answer any questions that you may have.

Why have I been chosen?
We are inviting all patients that meet the criteria for the main trial but do not wish to take part in that trial, to have their progress monitored. Information about your progress is very useful to us even if you decide not to take part in the trial.

Being part of the ‘follow-up only’ group will not affect your choice of treatment.

What information will be collected?
We will ask that you complete some questionnaires at the beginning of your treatment. When you come back to clinic for follow-up, we will ask you to fill out the same questionnaires at four, eight and twelve months after the start of your
treatment. The questionnaires will ask about your knee function and your general well being.

In addition we would like to collect data from your ‘magnetic resonance imaging’ MRI scan at the beginning of treatment and 1 year after treatment has started. These scans would be performed whether you enter the study or not and would not involve any additional hospital visits.

**Do I have to take part?**
It is up to you whether you take part. If you decide to take part you will be asked to sign a consent form. If you decide to take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

**Will my taking part in this study be kept confidential?**
All the information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

**Contacts for further information**
If, at any time, you would like further information about this research project you may contact the chief investigator Nicholas Smith on telephone number 02476968622. For independent advice contact the PALS service (Patient Advice Liaison Service) at Freephone 0800 0284203.
Appendix H: Consent forms for the MeTEOR study

Clinical trial of meniscal transplantation compared to personalised knee therapy Chief Investigator: Nicholas Smith

CONSENT FORM

Initial box

1- I confirm that I have read and understand the information sheet dated 01st September 2013 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

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 relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my records.

4- I understand that appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my
health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.

5- I agree to my GP being informed of my participation in the study.

6- I agree to take part in the above study.

<table>
<thead>
<tr>
<th>Name of patient</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>……………………..</td>
<td>…………..</td>
<td>……………..</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of person taking consent</th>
<th>Date</th>
<th>Signature</th>
<th>Role/Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>…………………………</td>
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<td>……………………………..</td>
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</tr>
</tbody>
</table>

Patient ID Number: __________

**Clinical trial of meniscal transplantation compared to personalised knee therapy FOLLOW UP ONLY**

Chief Investigator: Nicholas Smith

**CONSENT FORM**

7- I confirm that I have read and understand the information sheet dated 17th July 2013 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
8- 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.

9- I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my records.

10- I understand that appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.

11- I agree to take part in the above study.

Name of patient Date Signature

…………………….. ……….. ……………………………..

Name of person taking consent Date Signature Role/Title

…………………….. ……….. ……………………………..

……………………..
Appendix I: Intervention fidelity questionnaires for the MeTEOR study

Meniscal allograft transplantation

<table>
<thead>
<tr>
<th>Participant number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the participant have a meniscal transplant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was an NHSBT, RTI or Allosource graft used?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was an osteotomy performed if malalignment present?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other concurrent operative procedures?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was written rehab advise given?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were crutches given?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of physiotherapy sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for any deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other treatments?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Personalised knee therapy

<table>
<thead>
<tr>
<th>Participant number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a personalised knee therapy booklet given?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was an offloading brace given if malalignment present?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was there an initial treatment session with a senior knee physiotherapist at UHCW?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of physiotherapist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a written prescription given to the participant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many physiotherapy sessions did the participant have in total?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over how many months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for any deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other procedures?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix J: MRI protocol settings. * TEs for T2 map: 11.8, 23.6, 35.4, 47.3, 59.1, 70.9, 82.7, and 94.5 ms. Repetition time (TR), echo time (TE), field of view (FOV), number of excitations (NEX), proton density (PD), sagittal (sag), gradient recalled echo (GRE), coronal (cor), fat suppressed (FS).

<table>
<thead>
<tr>
<th></th>
<th>TR /ms</th>
<th>TE/ms</th>
<th>flip</th>
<th>FOV (cm)</th>
<th>Matrix</th>
<th>NEX</th>
<th>Thickness (mm)</th>
<th>Slices</th>
<th>Time</th>
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</thead>
<tbody>
<tr>
<td>PD Sag</td>
<td>2300</td>
<td>22.5</td>
<td>900</td>
<td>16</td>
<td>384x256</td>
<td>2</td>
<td>3.5/1.0</td>
<td>22</td>
<td>2.32</td>
</tr>
<tr>
<td>GRE Sag</td>
<td>440</td>
<td>12</td>
<td>200</td>
<td>16</td>
<td>320x224</td>
<td>2</td>
<td>3.5/1.0</td>
<td>22</td>
<td>3.21</td>
</tr>
<tr>
<td>T2 Sag</td>
<td>1000</td>
<td>*</td>
<td>900</td>
<td>16</td>
<td>256x160</td>
<td>1</td>
<td>3/0.6</td>
<td>27(x8)</td>
<td>8.07</td>
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<tr>
<td>Cube Sag</td>
<td>2960</td>
<td>18.4</td>
<td>900</td>
<td>16</td>
<td>256x256</td>
<td>0.5</td>
<td>1.4/-0.7</td>
<td>256</td>
<td>4.01</td>
</tr>
<tr>
<td>PDFS Cor</td>
<td>2000</td>
<td>22.8</td>
<td>900</td>
<td>16</td>
<td>352x256</td>
<td>2</td>
<td>3.5/1.0</td>
<td>23</td>
<td>2.32</td>
</tr>
</tbody>
</table>
Appendix K: Audit report from the sponsors for the MeTEOR study.

Dear Mr Nick Smith,

Re: MeTEOR – Meniscal transplantation and its Effects on Osteoarthritis Risk

An audit of the MeTEOR trial documentation held at the Clinical Sciences Building, UHCW was undertaken on 13 August 2014 on behalf of the University of Warwick and UHCW NHS Trust as trial co-sponsors, by myself and Isabella Petrie, Research Governance Manager, UHCW. I would like to thank you for your time and cooperation during the visit.

The trial documentation was found to be maintained to a good standard, with all approvals in place.

A summary of the findings is given below.

Findings are classified as follows:

- **Major**: those that pose an immediate threat to participant safety / trial integrity
- **Moderate**: those that compromise the integrity of certain components of the trial
- **Minor**: those that show lack of due diligence but do not directly compromise the trials’ conduct

Full definitions can be found in WCTU SOP 25: Auditing of Clinical Trial.

<table>
<thead>
<tr>
<th>No.</th>
<th>Finding</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Major findings</td>
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</table>

Moderate Findings

<table>
<thead>
<tr>
<th>No.</th>
<th>Finding</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No Moderate findings</td>
<td></td>
</tr>
</tbody>
</table>

Minor Findings
<table>
<thead>
<tr>
<th>No.</th>
<th>Finding</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Version 1 of the PIS (RCT) submitted with the initial application to the REC is not present on file.</td>
<td>Print off and file - score through and mark as superseded.</td>
</tr>
<tr>
<td>2.</td>
<td>The NHS REC application form on file is incomplete (only 13 pages present) with the signature pages missing.</td>
<td>Print off and file the complete, signed application form and file.</td>
</tr>
<tr>
<td>3.</td>
<td>Evidence of trial initiation training is present for all on the delegation log apart from C Lawrence.</td>
<td>Document and file details of training provided to C Lawrence.</td>
</tr>
<tr>
<td>4.</td>
<td>The PI signatures on the trial delegation log have not been dated as per GCP.</td>
<td>PI to add relevant dates to the delegation log.</td>
</tr>
</tbody>
</table>

**Notes:**

- Details of the funding body and organisation managing a research project is a HRA required element for inclusion in a PIS. These details are missing from the MeTEOR information sheets and should be included if any amendments are made to these documents in the future.
- Some of the text in the Safety Reporting section of the protocol is incorrect. This has been discussed with the CI and other orthopaedic group trial coordinators and managers and some standard text will be produced to be used in future protocols.
- Data entry checks were discussed and will be undertaken and documented by the trial coordinator before the final participant is recruited.

A written response to these findings to confirm that these actions have been completed should be returned to me by Friday 19 September 2014 and cc’d to Isabella Petrie, UHCW Research Governance Manager and Graham Hewitt WMS REGM.

Yours sincerely,

Claire Daffern
Quality Assurance Manager
Warwick Clinical Trials Unit
References


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220. Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ.* 2014;348:g3387.


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