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The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/48/01. The contractual start date was in July 2005. The draft report began editorial review in November 2008 and was accepted for publication in August 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Effectiveness and cost-effectiveness of arthroscopic lavage in the treatment of osteoarthritis of the knee: a mixed methods study of the feasibility of conducting a surgical placebo-controlled trial (the KORAL study)

MK Campbell,[1*] ZC Skea,[1] AG Sutherland,[2] BH Cuthbertson,[1] VA Entwistle,[3] AM McDonald,[1] JD Norrie,[1] RV Carlson,[4] S Bridgman[5] and the KORAL study group

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Objectives: To ascertain the acceptability of a randomised controlled trial comparing arthroscopic lavage with a placebo-surgical procedure for the management of osteoarthritis of the knee; and to assess the practical feasibility of mounting such a multicentre placebo-controlled trial.
Design: Mixed methods study including: focus groups with surgeons and anaesthetists; focus groups and interviews with potential participants; interviews with chairpersons of UK Multicentre Research Ethics Committees (MRECs); surveys of surgeons and anaesthetists; and a two-centre, three-arm pilot.
Setting: UK secondary care.
Participants: Members of the British Association of Surgeons of the Knee and members of the British Society of Orthopaedic Anaesthetists took part in the focus groups and surveys. Surgeons and anaesthetists from two regional centres in the UK also contributed to focus groups, as did patients from consultant lists in two UK regional centres, and members of *Arthritis Care*. Chairpersons of six UK MRECs were interviewed. Participants were eligible for the pilot if they were adults (18 years or older) with radiological evidence of osteoarthritis of the knee who might be considered for arthroscopic lavage, and were fit for general anaesthetic (defined by the American Society of Anaesthesiologists grades 1 and 2), and able to give informed consent.
Interventions: Participants in the pilot study were randomised to arthrosocopic lavage (with or without debridement at the clinical discretion of the surgeon); placebo surgery; or non-operative management with specialist reassessment.
Main outcome measures: The acceptability and feasibility of mounting a placebo-controlled trial for the evaluation of knee arthroscopic lavage.
Results: There was broad acceptance across all stakeholder groups of the need to find out more about the effectiveness of arthroscopic lavage. Despite this there was variation in opinion within all the groups about how researchers should approach this and whether or not it would be acceptable to investigate using placebo surgery. Within the health professional groups, there tended to be a split between those who were strongly opposed to the inclusion of a placebo surgery arm and those who were more in favour. For prospective trial participants who had osteoarthritis of the knee, the acceptability of the trial was discussed from a more individual perspective – reflecting on their personal reasons for or against participating. The majority of this group said they would consider taking part. The pilot study showed that, in principle, a placebo-controlled trial could be conducted. It showed that patients were willing to participate in a trial which would involve a placebo-surgical arm and that it was possible to undertake placebo surgery successfully and to blind patients to their allocation – although once patients knew their allocation, some patients allocated to surgery became more concerned about the possibility of undergoing placebo surgery, and withdrew. The experience of the pilot, however, showed that, despite full MREC approval, the study required major discussion and negotiation before local clinical approvals could be obtained. The fact that ethics approval had

been granted did not mean that clinicians would automatically accept that the process was ethical.
Conclusions: The study showed that, in principle, a placebo-controlled trial of arthroscopic lavage could be conducted in the UK, albeit with difficulty. Against the background of falling use of arthroscopic lavage the decision was, therefore, taken not to proceed to full-scale trial for this procedure. The study showed that for some health professionals the use of placebo surgery can never be justified. It highlighted the importance of the surgeon–anaesthetist relationship in this context and how acceptance of the trial design by both parties is essential to successful participation. It also highlighted the importance of informed consent for trial participants and the strength and influence of individuals' ethical perspectives in addition to collective ethics provided by MRECs.
Trial registration: Current Controlled Trials ISRCTN02328576.

Contents

List of abbreviations

AMA	American Medical Association
ASA	American Society of Anaesthesiologists
BASK	British Association of Surgeons of the Knee
BSOA	British Society of Orthopaedic Anaesthetists
CHaRT	Centre for Healthcare Randomised Trials
DMC(s)	data monitoring committee(s)
ECT	electro-convulsive therapy
EQ-5D	EuroQol-5 dimensions (quality of life instrument)
HES	hospital episode statistics
HTA	Health Technology Assessment
IQR	interquartile range
KORAL	Knee Osteoarthritis: Role of Arthroscopic Lavage
MREC(s)	Multicentre Research Ethics Committee(s)
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre (formerly known as NCCHTA)
NIHR	National Institute for Health Research
RCT(s)	randomised controlled trial(s)
SD	standard deviation
SF-12	Short Form (12 questions)

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), has been used only once, or is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Osteoarthritis is the most common form of arthritis in Western populations. When medication for osteoarthritis of the knee does not sufficiently relieve symptoms, the surgical procedure of arthroscopic lavage may be undertaken. Arthroscopic lavage involves washing out the joint space during arthroscopy, with additional debridement (the mechanical removal of debris and the trimming of rough surfaces) if deemed necessary. The evidence for the effectiveness of arthroscopic lavage is variable, however, and the largest trial conducted to date showed no evidence of a benefit of arthroscopic lavage or debridement over placebo. The generalisability of the results of this trial has been questioned as all procedures were performed by a single surgeon, a significant proportion of patients had severe arthritis, and the primary outcome was based on a non-validated instrument. Given the widespread use, high cost and continuing uncertainty around the effectiveness of arthroscopic lavage for osteoarthritis of the knee, the Health Technology Assessment (HTA) programme sought to commission a similar placebo-controlled trial of arthroscopic lavage in the UK. Recognising that there might be difficulties of mounting such a trial (in terms of perceived acceptability of the placebo design) the research was commissioned with an integrated, yet discrete, feasibility study, which is described in this monograph.

Objectives

The objectives of the feasibility study were two-fold: (a) to ascertain the acceptability of a randomised controlled trial comparing arthroscopic lavage with a placebo surgical procedure for the management of osteoarthritis of the knee; and (b) to assess the practical feasibility, through the conduct of a formal pilot study, of mounting such a multicentre placebo-controlled trial. This included assessing the acceptability of the proposed trial processes to patients and staff, to estimate the proportion of patients who would accept randomisation within the trial, and to examine the acceptability of the trial information material to patients.

Methods

The initial exploration of acceptability comprised: focus groups with surgeons and anaesthetists; focus groups and interviews with potential participants; interviews with chairpersons of the UK Multicentre Research Ethics Committees (MRECs); and surveys of surgeons and anaesthetists.

The pilot study was designed as a two-centre, three-arm trial of arthroscopic lavage (with or without debridement at the clinical discretion of the surgeon); placebo surgery; and non-operative (i.e. medical) management with specialist reassessment.

Results

There was broad acceptance across all stakeholder groups of the need to find out more about the effectiveness or otherwise of arthroscopic lavage. Despite this there was, however, variation in opinion within all the groups about how researchers should approach this and about whether or not it would be acceptable to investigate using placebo surgery. Within the health professional groups, there tended to be a split between those who were strongly opposed to the inclusion of a placebo surgery arm (on the grounds that it could lead to potential harms among individuals who could expect no personal benefit) and those who were more in favour on the grounds that they believed the small risks that relatively few people in a placebo surgery trial arm would be exposed to were justified because they were outweighed by the potential benefit (i.e. potential benefit to future patients and broader society through helping to ensure either that a demonstrably effective surgical procedure was used or that a demonstrably ineffective procedure was not). For prospective trial participants who had osteoarthritis of the knee, the acceptability of the trial was discussed from a more individual perspective – reflecting on their personal reasons for or against participating. The majority of this group said they would consider taking part. As well as expressing a desire to help others through their participation, there was a general tendency to down play any potential risk of harm from their participation whilst emphasising

the potential to gain some form of personal benefit. Given the nature of the proposed design, the health professionals and MREC chairpersons recognised that particular attention should be paid to the informed consent process when attempting to recruit participants.

The pilot study showed that, in principle, a placebo-controlled trial in surgery could be conducted. It showed that patients were willing to participate in a trial that would involve a placebo surgical arm, and that it was possible to undertake placebo surgery successfully and to blind patients to their allocation – although once patients knew their allocation, some patients allocated to surgery became more concerned about the possibility of undergoing placebo surgery, and withdrew. The experience of the pilot, however, showed that, despite full MREC approval, the study required major discussion and negotiation before local clinical approvals could be obtained. Many of the arguments raised at MREC level were raised again at local level, and the fact that ethics approval had been granted did not mean that clinicians would automatically accept that the process was ethical.

National trend data showed a slow decline in the usage of arthroscopic lavage over recent years.

Conclusions

The feasibility study showed that, in principle, a placebo-controlled trial of arthroscopic lavage could be conducted in the UK, albeit with difficulty. Against this background and a falling use of arthroscopic lavage, the decision was taken not to proceed to full-scale trial for this particular procedure.

The study showed that the placebo-controlled design remains controversial, and for some health professionals the use of placebo surgery can never be justified. It highlighted the importance of the surgeon–anaesthetist relationship in this context and how acceptance of the trial design by both parties is essential to successful participation. It also highlighted the importance of informed consent for trial participants and the strength and influence of individuals' ethical perspectives in addition to collective ethics provided by MRECs.

The wider lesson from the study is that the most favourable circumstances for a placebo-controlled trial in surgery are those where: (a) alternative designs would provide inferior (and potentially biased) results, particularly where the primary outcome is of a subjective nature and blinding cannot be sustained beyond the time of any placebo effect; (b) a placebo surgical procedure and type of anaesthesia can be devised that adequately mimic the active intervention with a level of intrusiveness and risk that is acceptable to surgeons, anaesthetists, ethics committees, and potential participants; (c) appropriate practical arrangements can be instituted in local centres to ensure that the delivery of such a design would be feasible; (d) sufficient numbers of potential participants (after assessment of clear descriptions and careful explanations in patient information leaflets of the advantages and disadvantages of taking part) judge for themselves that the risk-to-benefit ratio of participation is acceptable to them; and (e) levels of compliance with the allocation are sufficiently high to sustain scientific rigour.

Implications for practice

- A placebo-controlled trial of arthroscopic lavage could be conducted in the UK, albeit with difficulty.
- Those conducting trials in surgery must consider surgeon–anaesthetist partnerships when planning clinical trials, especially trials including a placebo arm.
- People taking part in, and those responsible for, authorising the conduct of trials have their own individual ethical perspectives which can influence their attitudes to research (in addition to the collective ethics assessment provided by MRECs). Researchers need to be aware of these, and work with them when planning clinical trials – especially trials involving a placebo arm.
- Terminology referring to 'placebos', 'shams', 'dummies', etc. each have different connotations that may influence participation.
- The importance of including clear descriptions and careful explanations in patient information leaflets was reinforced in this study. All trials should ensure that any advantages and disadvantages of participation are explained as fully as possible.
- Patient information leaflets within placebo-controlled trials should explicitly state that whilst benefit might be seen within a placebo group, the underlying mechanism of the placebo has no known direct effect.
- National arrangements for indemnity and non-negligent harm should be clarified for all researchers involved in the conduct of clinical trials, particularly those trials that might involve a placebo arm.

- The HTA programme should consider the routine use of staged funding (with integrated rapid decision-making) for more complex research projects.
- The optimal place for a placebo-controlled trial in surgery is likely to be where the strict conditions listed above can be satisfied.

Implications for research

- Research is required into the impact of different terminology referring to placebos (e.g. placebo, sham, dummy) on the understanding of the role and function of a placebo.
- Research is required into the usefulness of formal decision aids to aid participant consent in the context of a placebo-controlled trial.
- Research is required into the impact of individual versus collective ethics on the conduct of placebo-controlled trials.

Trial registration

This trial is registered as ISRCTN 02328576

Chapter 1
Introduction

Clinical background

Osteoarthritis

Osteoarthritis is a common and important cause of pain and disability and is the most frequent form of arthritis in Western populations.[1,2] Osteoarthritis of the knee results in disabling knee symptoms in an estimated 10% of people aged over 55 years.[3] A report from the World Health Organization, published in 1997,[4] suggested that osteoarthritis of the knee is likely to become the fourth most important cause of disability in women and the eighth most important in men. The aetiology of osteoarthritis of the knee is reported to be multifactorial, including general factors (such as age, sex and obesity), mechanical factors (such as trauma, recreational activities and alignment)[5,6] and genetic factors.[7] Knee osteoarthritis is characterised both by focal loss of articular cartilage and by central and marginal new bone formation (subchondral sclerosis, osteophytosis), but affects the whole joint.[5] There is often an associated low grade synovitis, but ligament laxity and muscle weakness about the joint are secondary changes, due to articular cartilage loss and disuse respectively. Clinically, knee osteoarthritis is associated with pain, joint stiffness and deformity, which lead to limitations of activities for sufferers. In 1977, Hernborg and Nilsson[8] demonstrated that the natural history of untreated osteoarthritis of the knee was one of gradual decline for most patients (over 10–18 years, 17% were improved, 26% unchanged and 56% worse clinically).

There is a range of treatment options available for the management of osteoarthritis of the knee, including non-pharmacological interventions (such as education, exercise, orthotic devices); pharmacological treatments (such as non-steroidal anti-inflammatory drugs, paracetamol, topical treatments); intra-articular modalities (such as corticosteroid and hyaluronic acid injections and tidal irrigation); and, surgical interventions (including therapeutic arthroscopy and ultimately joint replacement).[3] Current evidence to support the use of the various treatments is variable, although guidelines for the management of knee osteoarthritis have been produced.[3,9–11]

When pharmacological and non-invasive non-pharmacological treatments do not sufficiently relieve symptoms, arthroscopic lavage (with or without debridement) may be undertaken. Arthroscopic lavage involves washing out the joint space during arthroscopy with several litres of saline solution. Any intra-articular debris is then flushed out via arthroscopic cannulae. In addition, debridement may be undertaken during the same procedure. This involves the mechanical removal of debris and the trimming or shaving of rough surfaces that may interfere with the smooth movement of the joint. Arthroscopic debridement aims to remove any chemical or mechanical component that could contribute to the symptoms of osteoarthritis. It is reported that more than 650,000 of these procedures are performed each year in the USA – costing more than US$3.5 billion annually.[12] Hospital episode statistics (HES) for England for the financial year 2002–03 (the start of the project) indicated that approximately 34,000 therapeutic arthroscopic procedures of the knee were undertaken at an estimated annual cost to the NHS of over £34M[13] (although it is not possible to determine from the coding whether all procedures were for knee osteoarthritis).

Evidence for use of arthroscopic lavage

The evidence for the effectiveness of arthroscopic lavage is variable. The majority of reported studies of arthroscopic lavage are uncontrolled (mainly case series). Single studies have suggested that arthroscopic lavage and physiotherapy have benefit persisting to 6 months[14] when compared with physiotherapy alone, and simple (unguided) tidal irrigation is superior to medical management[15] and equivalent to arthroscopic debridement[16] in early osteoarthritis of the knee.

As arthroscopic treatment developed with the addition of debridement over lavage alone, further observational studies suggested that benefits persisted for up to 5 years,[17] particularly in knees with normal alignment,[18] minimal osteoarthritis[19] and meniscal tears,[20] and for patients with short-lived mechanical symptoms.[21] Different surgeons use ‘debridement’ to describe different procedures,

the studies are often small, with limited follow-up, and it is difficult to control for the placebo effect of any surgical intervention. The overall effect of generally positive results in 40–85% of patients is also not very different from the natural history outlined by Hernborg and Nilsson,[8] and many surgeons had come to the conclusion that arthroscopy and debridement should be reserved for those groups most likely to benefit (e.g. for those with meniscal tears).

More recently, however, there has been a small number of randomised controlled trials (RCTs) reported in the literature. In contrast to the uncontrolled studies, systematic reviews of these trials provide little evidence to support the routine use of arthroscopic lavage.[22,23] We have provided a brief summary of the trials[14,16,17,24–29] of arthroscopic lavage (with or without debridement) as identified from a search of MEDLINE and EMBASE until June 2008 in *Table 1*. We have not presented the details of trials of unguided lavage or trials that did not assess the independent effect of arthroscopic lavage from other treatments, e.g. trials of arthroscopic lavage plus intra-articular corticosteroids. Both a recent Cochrane review[30] and the National Institute for Health and Clinical Excellence (NICE) guidance[31] (both of which were published after the empirical research presented in this study was completed) also do not support the use of arthroscopic lavage, in non-discriminated osteoarthritis.

Specific studies have included trials of arthroscopic lavage against a placebo procedure, arthroscopic lavage against unguided irrigation, and arthroscopic lavage against other interventions for the management of knee osteoarthritis. Most of these trials involved small and selected groups of patients. For example, Forster and Shaw[26] reported an RCT of 32 patients randomised to arthroscopic lavage (with or without debridement as deemed necessary) versus hyaluronic acid intra-articular injection. This study showed no evidence of benefit of arthroscopic lavage at 12 months. Similarly, Chang *et al.*[16] compared arthroscopic lavage (with or without debridement as deemed necessary) against tidal irrigation in 32 patients, which again showed no evidence of greater improvement following arthroscopic lavage. Ward *et al.*[27] undertook a similar RCT in 51 patients comparing arthroscopic lavage with cannula lavage and also concluded that there was no evidence of a difference between the groups. In a controlled study by Livesley *et al.*,[14] however, which compared arthroscopic lavage plus physiotherapy with physiotherapy alone in 61 patients, the authors found a statistically significantly greater reduction in pain in the lavage group.

The largest trial to date was conducted by Moseley *et al.*[24] in 2002. In this trial, 180 participants were randomised to arthroscopic lavage, arthroscopic debridement or placebo procedure. This trial is described in more detail in the following section.

The Moseley trial

In the trial by Moseley *et al.*,[24] 180 patients were recruited from a single Veterans Affairs Medical Centre and randomised to arthroscopic lavage, arthroscopic debridement or placebo procedure. Patients were deemed eligible for inclusion in the trial if they were: 75 years old or younger; had osteoarthritis of the knee as defined by the American College of Rheumatology; reported, on average, at least moderate knee pain (≥4 on a visual analogue scale ranging from 0 to 10) despite optimal medical treatment for at least 6 months; and had not undergone arthroscopy of the knee during the previous 2 years. Patients were stratified into three groups according to severity of osteoarthritis, and randomised within strata with a fixed block size of six using sealed, sequentially numbered stratum-specific envelopes. Treatment assignment was not revealed to the patient. The trial was initially designed as a superiority trial to detect the superiority of the arthroscopic procedures over the placebo procedure. When no evidence of superiority was observed (see results below) the trial team changed to the use of an equivalence testing framework.

Of the 180 patients who were randomised, 61 were allocated to the arthroscopic lavage group, 59 to the arthroscopic debridement group and 60 to the placebo group. Baseline characteristics were similar across trial groups. Across the trial, the majority of participants were male (93%) and had an average age of 52 years. Approximately 29% had early arthritis, 46% had moderate arthritis and 25% had severe arthritis.

All procedures were undertaken by a single surgeon. Patients in the lavage and debridement groups received standard general anaesthesia with endotracheal intubation whilst patients in the placebo group received a '… short-acting intravenous tranquilizer and an opioid and spontaneously breathed oxygen-enriched air …'. Lavage consisted of joint flushing with at least 10 litres of fluid, whereby any loose debris was

TABLE 1 *Randomised controlled trials of arthroscopic lavage (with or without debridement) in osteoarthritis patients*

Trial	Comparators	Primary outcome	Result
Moseley *et al.*, 2002[24] Double-blind RCT	Arthroscopic lavage (61 participants) vs arthroscopic lavage + debridement (59 participants) vs placebo (60 participants)	Pain at 24 months	All groups got better compared with baseline Neither active treatment differed from placebo at 12 months
Moseley *et al.*, 1996[25] RCT, pilot	Arthroscopic lavage (3 participants) vs arthroscopic debridement (2 participants) vs placebo (5 participants)	Various pain measures	All groups did well
Forster and Straw, 2003[26] RCT	Arthroscopic washout (± debridement as deemed necessary, $n = 15$ participants) vs 5 × weekly Hyalgan intra-articular injections ($n = 17$ participants)	Pain and function at 6 weeks, and 3, 6, and 12 months	Both groups improved pain from baseline No significant difference between groups at 12 months for pain Suggestion of improved function with injection
Livesley *et al.*, 1991[14] Controlled clinical trial	Arthroscopic lavage + physiotherapy (37 participants) vs physiotherapy only (24 participants)	Pain at 3, 6 and 12 months	Statistically significant greater reduction in pain in favour of lavage at 3 and 6 months No significant difference at 12 months Clinical importance unclear
Chang *et al.*, 1993[16] Blinded RCT	Arthroscopic lavage (± debridement) (18 participants) vs tidal irrigation (14 participants)	Pain and function	All groups improved compared with baseline No apparent difference between procedures at 12 months
Ward *et al.*, 1998[27] Abstract only, RCT	Arthroscopic lavage ($n = 51$ participants in total) vs cannula lavage	Pain and function	No significant difference in outcome
Gibson *et al.*, 1992[28] RCT	Arthroscopic lavage (10 participants) vs arthroscopic debridement (10 participants)	Quadriceps and hamstring power	No clinical improvement after either procedure Some improvement in muscle torque following lavage but not debridement
Hubbard, 1996[17] RCT	Arthroscopic lavage (36 participants) vs arthroscopic lavage + debridement (40 participants)	Pain at 1 year	More people pain-free in debridement group (5/36 vs 33/40) at 1 year ($p = 0.05$)
Kalunian *et al.*, 2000[29] Double-blind RCT	Arthroscopic lavage (full irrigation) (41 participants) vs arthroscopic lavage (minimal saline) (49 participants)	Pain	All groups improved compared with baseline Statistically significant difference in favour of full irrigation at 12 months ($p = 0.02$)

removed through arthroscopic cannulae. The debridement group also had any rough articular cartilage shaved, all torn or degenerated meniscal fragments trimmed and the remaining meniscus smoothed. For the placebo group, the knee was prepared for lavage and draped, and three 1-cm incisions made in the skin. To simulate the procedure, the surgeon asked for all instruments and manipulated the knee as if arthroscopy was being performed. Saline was splashed to simulate the sounds of lavage; however, no instruments entered the portals for arthroscopy. The patient was kept in theatre for the amount of time a standard debridement would take.

The primary outcome for the study was knee-specific pain (measured over 24 months using a 12-item self-reported Knee Specific Pain Scale

created specifically for the study). Pain scores ranged from 0 to 100, with higher scores indicating more severe pain. The results showed that all groups improved from baseline at both 12 and 24 months. No significant differences were observed at follow-up, however, between the placebo group and either 'active' surgery group. For example, mean (± standard deviation) pain scores at 12 months were 48.9 ± 21.9, 54.8 ± 19.8 and 51.7 ± 22.4 for the placebo, lavage and debridement groups respectively. Scores at 24 months showed similar results, with pain scores of 51.6 ± 23.7, 53.7 ± 23.7 and 51.4 ± 23.2 for the placebo, lavage and debridement groups respectively.

Whilst the Moseley trial displayed high methodological rigour, the generalisability of the results has been questioned by a number of authors.[32,33] In particular, it was noted that only 56% of those eligible agreed to participate, and that participants had more severe arthritis, were younger, and were more likely to be white than non-participants. The lack of detail about the presence of mechanical symptoms, the degree of misalignment or limitation of motion and the grade of articular cartilage degeneration was also questioned,[33] as well as the potential generalisability of results from a population of elderly male veterans. The use of a non-validated instrument to assess pain (the Knee Specific Pain Scale), and the statistical appropriateness of converting what started as a superiority trial to an equivalence trial, with attendant issues over power calculation, were specifically challenged,[34] although these were defended by the Moseley group.[35]

The commissioned research

It was against this background that the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme sought to commission a new RCT of the effectiveness and cost-effectiveness of arthroscopic lavage for the treatment of patients with osteoarthritis of the knee. Given the widespread use, high cost and uncertain effectiveness of arthroscopic lavage for osteoarthritis of the knee, there was a clear need for further robust research if future policy and practice relating to the use of this intervention were to be based on reliable evidence. Given the results of the Moseley trial, the HTA programme sought to commission a similar placebo-controlled trial of arthroscopic lavage in the UK.

Recognising that there may be potential difficulties in mounting a placebo-controlled surgical trial (in terms of perceived acceptability of such a trial design), the HTA programme commissioned the research with an integrated, but discrete, feasibility study. Progression to a full-scale placebo-controlled trial would only go ahead if the feasibility study showed that this was appropriate. For a full-scale trial to be conducted successfully in the UK, it would be necessary to identify enough surgical teams willing to deliver arthroscopic lavage (and a placebo version of it) in the context of a randomised trial, and to be confident that a sufficient proportion of eligible patients would, when well informed, be willing to take part in such a trial.

This monograph presents the findings of the feasibility study.

The research project

Reflecting the commissioning brief, the feasibility study – known as KORAL (Knee Osteoarthritis: the Role of Arthroscopic Lavage) – developed in four distinct phases:

- *Formal exploration of the acceptability of a placebo-controlled trial* – the aim of this phase was to ascertain the acceptability of a proposed RCT comparing arthroscopic lavage with a placebo surgical procedure for the management of osteoarthritis of the knee to key stakeholder groups. This involved four components: focus groups with health professionals; focus groups (and interviews) with potential participants; interviews with chairpersons of the UK Multicentre Research Ethics Committees (MRECs); and, surveys of surgeons and anaesthetists.
- *Obtaining ethics approval to mount a pilot RCT* – having identified the components of a possible placebo procedure, we sought ethics approval to conduct a formal pilot study to assess the full feasibility of mounting a multicentre placebo-controlled trial to evaluate the effectiveness of arthroscopic lavage for osteoarthritis of the knee. As it sought to reflect the design of a full trial, the pilot was to include full consent and randomisation to a placebo surgical arm. This raised a number of significant ethical issues.
- *The formal pilot* – the aim of the pilot study was to assess the practical feasibility of mounting a multicentre placebo-controlled trial to evaluate

the effectiveness of arthroscopic lavage for osteoarthritis of the knee. This included assessing the acceptability of proposed trial processes to patients and staff, to estimate the proportion of patients who would accept randomisation to the trial, and to examine the acceptability of the trial information material to patients. The pilot was designed as a two-centre, three-arm trial of: a) arthroscopic lavage (with or without debridement at the clinical discretion of the surgeon); b) placebo surgery; and c) non-operative (i.e. medical) management with specialist reassessment.

- *The decision-making process as to whether to progress to full trial* – based on the insights gained from the previous three phases and from external evidence, a decision was made jointly with the HTA programme on whether a full placebo-controlled trial should be mounted.

At the start of the project, the KORAL team convened a study day for the grant applicants, project staff and invited experts to further develop the study protocol. This study day (held in March 2005) benefited significantly from a presentation and discussion by Dr Nelda Wray, who was the chief investigator (and Dr Carol Ashton, a co-investigator) of the Moseley trial.[24] Professor Paul Dieppe (an acknowledged UK expert on osteoarthritis) also contributed.

The four phases of the feasibility study are described in Chapters 2–5. In Chapter 6, the implications of the project are discussed as a whole, finishing with a summary of the implications for practice and recommendations for further research.

Chapter 2

Formal exploration of the acceptability of a placebo-controlled trial

Aim

The aim of this first phase of the research was to ascertain the acceptability of a proposed RCT comparing arthroscopic lavage with a placebo surgical procedure for the management of osteoarthritis of the knee to key stakeholder groups (in particular surgeons, anaesthetists, prospective participants and members of research ethics committees).

Objectives

- To ascertain what is the range of placebo procedures that could be considered for a trial comparing arthroscopic lavage with a placebo procedure.
- To describe the attitude of important stakeholder groups (in particular, surgeons, anaesthetists, prospective participants and members of ethics committees) to the use of a placebo procedure in the proposed evaluation.
- To clarify whether attitudes to the proposed trial differ depending on the type of placebo proposed and/or key trial design features.

This initial phase of research comprised four main components that sequentially allowed us to build a picture of the likely acceptability of a trial to evaluate the effectiveness of arthroscopic lavage in comparison with a placebo procedure:

- *Component 1: Focus groups with health professionals* – we conducted exploratory focus groups with health-professional stakeholders (surgeons and anaesthetists) to identify the range of placebo procedures that may be used, and to appraise their strengths and weaknesses from a clinical perspective.
- *Component 2: Focus group and interviews with people with osteoarthritis* – we also conducted exploratory focus groups and interviews with people with osteoarthritis of the knee to allow us to identify the types of judgements, beliefs and attitudes (including concern) that patients and prospective trial participants may hold in relation to a proposed trial; to identify features of the placebo procedure and trial design that could enhance the acceptability of the trial to potential participants; and to test and refine an initial draft of written information for potential participants. (The initial draft was developed taking into account the views expressed by the surgeons and anaesthetists on the most appropriate form of placebo surgery. It was designed with input from Arthritis Care.)
- *Component 3: Interviews with chairpersons of UK MRECs* – chairpersons of MRECs were interviewed by telephone. Their opinions were sought on the ethical issues raised by the research proposal. Twelve ethics committee chairpersons were invited to take part in the research.
- *Component 4: Surveys of health professionals* – Postal surveys of orthopaedic surgeons (all members of the British Association of Surgeons of the Knee; BASK) and anaesthetists (all members of the British Society of Orthopaedic Anaesthetists; BSOA) were conducted. The aim of these surveys was to investigate the distribution of attitudes towards the proposed trial and ascertain rates of expressed willingness among these groups to support the trial in their professional capacity.

The methods and findings of each component are described in separate sections below.

Full MREC approval was received for this phase of the study. To preserve independence with regard to any future ethics decisions about KORAL, the chairperson of the MREC who approved this part of the study was not interviewed for Component 3 of the study.

Component 1A – Focus groups with health professionals: the orthopaedic surgeons

Methods

Two surgeon focus groups were conducted at the annual meeting of the British Orthopaedic Association meeting, which was held in Birmingham in September 2005. Three orthopaedic surgeons contributed to the first focus group ('Group A') held at the British Orthopaedic Association meeting, only one of whom had no prior association with the KORAL team. Fifteen orthopaedic surgeons contributed to the second focus group ('Group B') held at this meeting – giving a total of 16 surgeons. In addition, we held a focus group ('Group C') in a regional centre in October 2005 where 25 local orthopaedic surgeons contributed.

Focus group content

The focus groups with orthopaedic surgeons were facilitated primarily by the lead orthopaedic surgeon on the KORAL team (AGS), with assistance from a selection of other members of the research team (ZCS, MKC, VAE or JDH). The topic guide formulated for use within this focus group is presented in Appendix 1.

After initial introductions, an orthopaedic surgeon from the KORAL team gave a short presentation (see Appendix 2) that summarised the current research evidence of the effectiveness of arthroscopic lavage (including a description of the process and findings of the trial conducted by Moseley *et al.*[24]); presented the rationale for conducting another placebo-controlled RCT to evaluate the procedure; and explained that the current discussion was being conducted to help assess the acceptability and feasibility of such a trial and help inform the development of the placebo procedure. Focus group participants were made aware that approximately 34,000 of these procedures were being carried out annually at a cost to the NHS of approximately £34M. The groups were then encouraged to discuss their views about the acceptability of the proposed placebo-controlled trial, design features that would make it more or less acceptable, and what kind of placebo would be most appropriate if the trial went ahead. Throughout the discussions, the facilitator(s) answered questions of clarification and repeated information about the Moseley trial and the current feasibility study as required.

We did not attempt to elicit individuals' attitudes towards the proposed trial in a systematic and quantifiable way, focusing at this stage on identifying the types of consideration that could contribute to their assessments of the trial's acceptability and feasibility. However, the facilitators did on several occasions ask for a 'show of hands' indication of agreement with specific proposals, and impressions of consensus are indicated in the findings below.

Analytic procedures

The three focus group discussions were recorded and transcribed. The transcripts were then analysed thematically using a modified Framework approach.[36] Following initial familiarisation with the transcripts, the data were coded according to a series of broad themes that reflected both the main research questions and the key issues that emerged in discussions. Charts were created to summarise the data relating to each broad theme, and these were used to develop a characterisation of the range of beliefs and opinions expressed by the orthopaedic surgeons on issues salient to the acceptability and feasibility of the proposed placebo-controlled trial.

Findings

The balance of attitudes towards the proposed trial differed across the three discussion groups. In the first focus group, the only surgeon who did not have a previous association with the KORAL team accepted the rationale behind the proposal, but was uncomfortable with the inclusion of a placebo surgery arm; whilst in the second focus group, the majority of the participants spoke in favour of the proposed trial and indicated willingness to participate. At the regional centre discussion, attitudes were more mixed and, in a show of hands at the end of the discussion, about half of those present indicated potential willingness to recruit patients to a two-arm trial (arthroscopic lavage versus placebo surgery), and a few more indicated potential willingness to recruit patients to a three-arm trial (arthroscopic lavage versus placebo surgery versus conservative management).

The key considerations that featured in discussions about the acceptability of a trial that included a placebo surgery arm included:

- surgeons' current practices and beliefs about the effectiveness of arthroscopic lavage and alternatives

- surgeons' beliefs about the acceptability of conducting placebo surgery
- concerns about the usefulness of information that might be generated by a placebo-controlled trial of arthroscopic lavage
- aspects of trial methodology/trial results that would be necessary to convince surgeons to modify practice.

Surgeons' current practices and beliefs about the effectiveness of arthroscopic lavage and alternatives

Most participating surgeons stated that they did not routinely perform arthroscopic lavage for therapeutic purposes, although one surgeon did offer it routinely, others performed it occasionally, and several had conducted it previously or had worked for consultants who did.

The reasons given for not routinely performing arthroscopic lavage included a conviction that the procedure was ineffective for symptom improvement. For example:

> I think we do accept that by just washing it out, what we call lavage, is not clinically effective. I mean that's almost accepted practice … we think its actually quite pointless washing a fully worn out [joint] at all.
>
> (Surgeon 6, Group B)

Beliefs about the lack of effectiveness of arthroscopic lavage derived from several sources, including the surgeons' own or others' clinical observations of patients 'all coming back' with continuing problems after the procedure. Some surgeons thought these observations had caused a decline in the use of arthroscopic lavage that started before the publication of the Moseley trial, although for others, the findings of this trial had been influential.

There was some disagreement within the groups about how the findings of the Moseley trial should be interpreted and responded to, and several surgeons pointed out that there was some evidence (from both the scientific literature and their own observations) that arthroscopic lavage might offer at least short-term pain relief. They were thus reluctant to dismiss it as always or completely ineffective:

> Well there is some proof. There's limited proof it's beneficial. There are some papers that say it is …
>
> (Surgeon 2, Group B)

> If … you end up washing the knee out, sometimes the symptoms do improve and make it pseudo-working. We had a lady recently, and she had a defect, and she's a lot better since we washed the knee out, that's 3 weeks ago now.
>
> (Surgeon 1, Group C)

The potential usefulness of arthroscopic lavage was in part considered in relation to other options for managing osteoarthritis of the knee. There was consensus that conservative management, including physiotherapy, often did not provide satisfactory long-term pain relief. There was also consensus that knee replacements could provide effective relief – although they also carried significant risks and had a limited lifespan. In this context, some surgeons considered arthroscopic lavage (positively) as an intervention that may be used to delay knee replacement surgery, or that could be offered as 'something' to patients whose pain and/or mobility problems had not been adequately relieved by conservative management but who might not be eligible for knee replacement. For example:

> Surely 6 months of free from symptoms for people with early OA [osteoarthritis] who wouldn't be going on to get a surgical procedure to help them is actually worthwhile isn't it?
>
> (Surgeon 7, Group C)

> But if you take the alternative view that there are patients at present who are having knee replacements with all the potential risks of those unnecessarily, because they could have been, sort of, lasted out with a couple of wash outs then, that's quite a …
>
> (Surgeon 4, Group B)

The one surgeon who clearly stated that he routinely performed arthroscopic lavage explained that, whilst he accepted that the scientific evidence was unclear with regard to the procedure's long-term effectiveness, he thought the intervention was theoretically plausible, and was inclined to accede to requests from patients who believed or hoped that some kind of surgery would help relieve their symptoms:

> But at present we believe that it does at least theoretically you wash out the synovial and you see physically that … the synovial fluid does not look healthy somehow, it looks murky, so it must do some good. So we think it must do some good to this patient.
>
> (Surgeon 1, Group A)

> If you tell them that you don't need an operation then they go to the doctor [saying] 'You want me to live with the pain like this?' … They want something positive from it, whether it works or not that is a different matter … All that we can offer is to give them some kind of surgical procedure that we think might help … If you don't offer them operation they don't like you at all, they want an operation.
>
> (Surgeon 1, Group A)

For others, however, using arthroscopic lavage as a 'delaying' intervention (in terms of knee replacement procedures) carried significant opportunity costs:

> If the trial shows they have got short-term relief of symptoms after the lavage or debridement you know the thing then is we are postponing their total knee replacement for maybe 6 months or 12 months at the expense of doing many more extra operations using good time … and hence we've wasted valuable resources and time to postpone the inevitable for about 6 or 12 months … If after 6 months their symptoms come back to the same level then do you then contemplate arthroplasty of any form or do you do a total knee replacement. You've in fact just postponed the surgery for 6 months. At the expense of an extra operation and then you are going to do much more extra operations.
>
> (Surgeon 2, Group C)

One surgeon also commented that providing (ineffective) arthroscopic lavage procedures would encourage patients to want more (knee replacement) surgery:

> Trouble is, once you've operated, even if they get better for a while, when they then come back, they are very reluctant to be put off for any longer, you know, they've got the notion that surgery is the answer to their problem, even if they are not really quite at the stage where they would appreciate a disappointing result from a knee replacement, you know, but by that time, they have had an operation, and you have then convinced them that surgery is a good thing to do, and they won't be put off, that's why I've stopped doing it.
>
> (Surgeon 8, Group B)

Surgeons' beliefs about the acceptability of conducting placebo surgery

All the surgeons, whether they were more or less inclined to be optimistic about the effectiveness of arthroscopic lavage, generally supported the view that it was important to conduct research to remove the current uncertainty about this. Their support derived from a conviction that surgery should be more evidence-based, and from a concern that if significant numbers of surgical procedures were being conducted that were delivering little or no benefit, this could represent a serious waste of NHS resources:

> Well, the general principle. A lot of what we do is completely unproven and we need to accept that as surgeons. Our physician colleagues, however much we slag them off, do actually use drugs which have been proven to have an effect … We are doing some procedures for which there is no evidence at all, except 'I've got this great operation' and then its such and such's operation forever more. So I think there is a strong need for better control, blinded trials in surgery … It is important. This needs to be done. Long overdue, long overdue.
>
> (Surgeon 8, Group B)

> Health services resources. Because if you are doing an operation that has very marginal benefit, it's entirely placebo benefit, can we afford to be doing 34,000 operations a year that are essentially glorified acupuncture?
>
> (Surgeon 4, Group C)

However, not everyone agreed that a placebo-controlled RCT was either appropriate or feasible. Objections to the inclusion of a placebo surgery arm were based on ethical concerns about exposing people in this arm to the risk of anaesthesia and possibly health-care acquired infection, and concerns about the practical implications and usefulness of the findings of such a trial.

Some surgeons were strongly opposed to the inclusion of a placebo surgery arm on the grounds that it could lead to potential harms among individuals who could expect no benefit:

> Theoretically there is the possibility of harming the patient. Without deriving any benefit from it. Somebody could die from it.
>
> (Surgeon 1, Group A)

> I've got serious concern by doing a placebo, sham operation, and I would never participate as a patient in that and I would never like to subject a patient to that. Because there is no surgical operation or anaesthetic that is risk free. And even if 1 out of 100,000 patients, or 10,000 patients should suffer from an

> anaesthetic, I think that raises a whole range of ethical issues … It's not a non-invasive procedure that you do,… even a placebo is invasive. It's not like giving glucose tablets which are non-invasive. It is not withholding treatment, it is invading somebody, it is in fact doing something, which can be potentially harmful which is the contentious and ethical issue for me.
>
> (Surgeon 2, Group C)

(This latter surgeon did not think his ethical concerns would be removed if there was evidence that patients experienced symptomatic relief from the placebo procedure.)

Some surgeons' general inclinations to be concerned about placebo surgery were mitigated in the specific context of the proposed trial to evaluate arthroscopic lavage because the subjective, and perhaps subtle, nature of the effects of the procedure made it harder than other surgical interventions to evaluate without a placebo and because the procedure could be mimicked relatively easily:

> If you are looking at trials where people have carpal tunnel release to people who have not had carpal tunnel release etc. carried out, the benefits gained from the release is not marginal. What most people would describe as marginal. Whereas we are looking at a situation here where the benefit is so marginal, we need this sort of study to find out.
>
> (Surgeon 3, Group C)

> [Facilitator] So you think that basically a placebo surgery would only be appropriate in a situation where the benefit of the operation is relatively marginal? And where there is a clear benefit it will be inappropriate? [Sounds of agreement from participants]
>
> Where there is a clear benefit you don't need these sorts of studies. It's ethically unacceptable to do it.
>
> (Surgeon 3, Group C)

Some surgeons were less concerned about the ethics of placebo surgery when they focused primarily on a procedure that involved them making skin-deep incisions only (thus reducing the risk of introducing infection into the knee joint, which some thought was low anyway):

> To get back to the question, from a purely surgical viewpoint, would we be happy to make two nicks and do nothing else, from a surgical viewpoint? I mean I would. [Sounds of agreement from around the table] I don't have any problems with the ethics … There are guys who have done probably 5000 arthroscopies and never had a single problem.
>
> (Surgeon 7, Group B)

> The sham incision is nothing, I mean who cares if you have a little scratch on your knee …
>
> (Surgeon 2, Group B)

> Arthroscopies are relatively easy compared with others because you are only making small cuts, but for many other operations, knee replacements, hip replacements, you'd be making a very large incision, and I think making a large incision would be ethically less acceptable to many surgeons, including me …
>
> (Surgeon 3, Group C)

However, they did acknowledge that the risks of general anaesthesia would make the use of placebo surgery less acceptable to anaesthetists and ethics committees.

Some surgeons who did not routinely offer arthroscopic lavage themselves (or worked in centres where arthroscopic lavage was rarely performed) raised particular concerns about the ethics of their own (or their centre's) participation. Their concerns related to (1) the potential lack of equipoise locally, (2) the fact that if they or their centre were to participate in the proposed trial, patients in both placebo and active surgery arms would be exposed to risks that they would not normally have been exposed to, (3) the potential lack of (or lesser) skill among surgeons who had not been offering the procedure, and (4) the implications for surgical waiting lists of adding extra procedures to theatre lists.

For example:

> We are a unit who do very few of these procedures, so we are going to be recruiting people who another time would never have the operation at all, whether or not they get the placebo. And that's one of the problems about doing it in this unit is we start off by doing very few of these procedures deliberately and so we would be recruiting people we wouldn't have ever been subjecting to an anaesthetic.
>
> (Surgeon 4, Group C)

Concerns about the usefulness of information that may be generated by a placebo-controlled trial of arthroscopic lavage

The surgeons who spoke in favour of a placebo-controlled trial tended to focus on a consideration of the potential benefits to future patients and broader society (at least a national level) of helping to ensure either that a demonstrably effective surgical procedure was used or that a demonstrably ineffective procedure was not. For some, consequentialist reasoning made the small risks that relatively few people in a placebo surgery trial arm would be exposed to justifiable because they were outweighed by the potential benefit:

> Some people will perhaps have an anaesthetic complication who has had a placebo operation. But if the trial is a useful trial, then in the grand scheme of things it may actually prevent many people having anaesthetic risks or deaths for a procedure that may not actually have any benefit.
>
> (Surgeon 1, Group C)

However, not all were convinced that the proposed trial would deliver such useful knowledge. In part, their views depended on the kinds of findings they envisaged, and on their views of how these would or should be interpreted.

Although no surgeon disputed the rationale for wanting to investigate the effectiveness or otherwise of arthroscopic lavage, there was extensive debate among the surgeons about whether comparing arthroscopic lavage with conservative management might be more appropriate from an ethical and/or methodological perspective. Some focused on the potential of this design to avoid the ethical issues surrounding placebo surgery, whereas others questioned whether incorporating placebo surgery would really provide a 'definitive' answer about effectiveness. For example:

> It would be more ethically correct to compare doing nothing to a lavage first and then look at the results and see … You don't need to know the benefits of the placebo, it's irrelevant. When you make a clinical decision, you have to decide whether it's lavage or not. And so all you need to know is benefit from lavage and benefit from not doing anything and if the benefit from the lavage is marginal, then you don't do lavage and that's all that you need to do …
>
> I think what we need to establish first of all is what benefits if any you get from arthroscopic lavage is essentially small studies and if you do a larger study to confirm that you do get some benefits from arthroscopic lavage then you need to establish is it the placebo or is it not. You need to establish first of all that you do get benefit from arthroscopic lavage.
>
> (Surgeon 3, Group C)
>
> I was just wondering what we are actually trying to prove by having a placebo arm in arthroscopic lavage? Whether arthroscopic lavage work better than placebos? At the end of the day we don't even know if arthroscopic lavage is better than leaving the patient on the conservative treatment.
>
> (Surgeon 11, Group C)
>
> What you need to do first is a decent study to actually look at conservative versus operative and then once you've done that decent study, can you consider putting people at risk of placebo operations.
>
> (Surgeon 10, Group C)

Other surgeons disagreed, however, arguing firstly that there was no need to make this comparison because: (a) conservative management would have already proven ineffective in patients considered suitable for lavage; and (b) this comparison has already been made in previous research. Some also argued that there was a methodological need for a placebo surgical trial because: (a) a placebo component is needed to detect a small difference between the groups; and (b) a placebo is needed to attempt to disentangle what (if any) aspect of the arthroscopic lavage procedure is having a positive effect. For example:

(a) Conservative management would have already proven ineffective in patients considered suitable for lavage:

> That should have already been worked through because the indication would be the failure of management. Everyone gets the same sort of spiel when they come to my clinic and I'm sure we all do that, registrars might forget to do it but …
>
> (Surgeon 4, Group B)
>
> [Facilitator] So that should be dealt with already, because the reason they come to you are because medical management has failed?
>
> Yes
>
> (Surgeon 7, Group B)

(b) Comparison of arthroscopic lavage with conservative management has already been done:

> But that work [trials of arthroscopic lavage versus conservative management] has been done in the past…
>
> (Surgeon 2, Group C)

> That's been done hasn't it? Somebody's looked at the effect of physio on this kind of stuff so you don't need to go over that ground, because we are trying to answer the question that we started asking.
>
> (Surgeon 4, Group C)

(c) A placebo component is needed to detect a small difference between the groups:

> What you are saying is, the reason for using a placebo is that you're taking out another variable if your results are close. If your results, say you hadn't used a placebo and you just used a group that hadn't had an operation and you had enough numbers and there was a big enough difference it wouldn't matter that you hadn't had a placebo, what you are assuming by using a placebo is that your going to prove a smaller difference possibly.
>
> (Surgeon 2, Group B)

> [Responding to being asked what would convince him that the 'best' trial had been conducted] If there is no placebo it's not a trial.
>
> (Surgeon 4, Group B)

(d) A placebo is needed to attempt to disentangle what (if any) aspect of the arthroscopic lavage procedure is having a positive effect:

> Well then you don't know whether or not it's washing out the knee or the fact they have got three cuts.
>
> (Surgeon 4, Group C)

Within these discussions about whether or not the proposed trial should omit the placebo component, there was also some discussion about the rationale of adding a third non-surgical management arm to a trial of arthroscopic lavage versus placebo. There was no clear consensus reached in the discussions about this, although arguments for the addition of a non-surgical management arm related to whether comparing placebo surgery alone with arthroscopic lavage would really provide a 'definitive' answer about effectiveness. For example:

> The thing is if, and lets say it finds out you just do a placebo with lavage or debridement and it says there is no difference between the two you're still none the wiser because actually people may still be better off having a debridement or nothing compared to actually having absolutely nothing. So the fact they think they have had surgery, you know the placebo effect has actually helped them, in which case they are actually better off having a lavage than nothing at all. You know. Was that not… You would have to conduct [a three-arm trial]. If you are trying to make decisions about what people do clinically later, I mean you are better off having. If they are no different between placebo and lavage we still don't know whether we are better off doing a lavage compared to doing absolutely nothing at all.
>
> (Surgeon 7, Group C)

> So a three arm? [Several sounds of agreement around table.]
>
> (Surgeon 12, Group C)

Aspects of trial methodology/trial results that would be necessary to convince surgeons to modify practice

When those who did not currently perform arthroscopic lavage were asked what kinds of effects they would need to see robustly demonstrated to be confident that it should be used in the NHS or to persuade them to reintroduce the procedure, they suggested they would be looking for significant symptom relief over a reasonable length of time:

> I think it's very important, in surgery more than anything, as compared with taking a tablet, I think it's quite appropriate for us to assume you get much bigger return for treatment, and hence I think, you are perfectly valid to say we will expect quite a sizeable difference in outcomes.
>
> (Surgeon 6, Group B)

> I think the most important thing would probably be a sustained integration of patients being symptom free…
>
> (Surgeon 2, Group C)

However, there was no clear consensus about the duration of benefit that would make arthroscopic lavage worthwhile, with opinions ranging from

3–4 months to 3–4 years. In part this reflected the divergence of views about the value of 'delaying' knee replacement surgery (as discussed above):

> … and then how long do the symptoms, how long is the patient symptom free for, is it 6 months, 12 months, 24 months? And whether that delay incoming to a joint replacement is worthwhile just for a 6-month benefit going through an extra procedure just for a benefit of 6 months, is that worthwhile as well?
>
> (Surgeon 2, Group C)

Participating surgeons were asked to consider what aspects of trial methodology would need to be put in place to convince them of the robustness of research investigating the effectiveness of arthroscopic lavage and, following on from this, to convince them to modify their practice in line with the results (whether favouring arthroscopic lavage or not). There tended to be agreement about the 'core' aspects that would make the trial a 'good' one. In addition to thinking that the trial should be conducted across multiple centres and large enough to be statistically powerful, the surgeons also discussed the following:

(a) Careful patient selection (age range, osteoarthritis status, symptoms, previous surgery):

> The case mix, you know the case selection would have to be very controlled, because they are a fairly wide spread bunch, you know, you've got things that enter into the equation like body mass index, whether they've got any joint space on weight-bearing films, have they got any mechanical symptoms?
>
> (Surgeon 11, Group B)

> The likely age group that you can manage in this way, there's no good answer to any way, is there. You know, so, the, if you're going to stick age limits on it, which I think would probably be a good idea … 40–55 or whatever, where there is, at the minute, there is that grey area, and it's very grey!
>
> (Surgeon 4, Group B)

> I think before you do that you need to classify what is early degenerative change you know, the criteria will have to be there because what may be early degenerative change for person A may not be early degenerative change for person B … And what is early OA [osteoarthritis]? The Americans do a joint replacement at a very earlier stage than we do. For us, what is early OA, advanced?
>
> (Surgeon 2, Group C)

(b) Being allowed to do what they normally do (importance of reflecting current practice, but acknowledgement that surgeons who do not routinely perform arthroscopic lavage would also need to be involved):

> If you're not doing what people are normally doing then you're not going to get an answer that means anything are you really? The only way that you're getting an answer that means anything is by including what people do normally, warts and all.
>
> (Surgeon 2, Group B)

> But if you've got a big enough trial, and you're looking at standard practice, and you add different types of hospitals, different types of surgeon, then you'd get the real answer then, because it's what's happening in the NHS practice.
>
> (Surgeon 4, Group B)

> Oh no, I agree. But I think it's fundamental for those of us who are a bit cynical about it to get involved.
>
> (Surgeon 8, Group B)

As part of this discussion, some surgeons also argued for a placebo component, but not everyone agreed (for the reasons outlined in the sections below).

Views about the design of the placebo

During the focus groups, there was extensive discussion of what an appropriate placebo might consist of (assuming that the proposed trial was to go ahead). Focusing on ways in which the placebo could best mimic arthroscopic lavage, whilst still ensuring that any risks of harm were minimised, the consensus was for three superficial cuts that would just pierce the epidermis. Avoidance of penetration of the knee capsule would reduce the risk of introducing infection, and help ensure that a lavage 'type' procedure was not inadvertently performed:

> No, you'd have to do the dermis … just enough to make it bleed.
>
> (Surgeon 8, Group B)

> If you put the scope in you introduce fluid therefore technically it becomes a lavage even if it's a tiny amount, doesn't it?
>
> [Several 'yes's]
>
> (Surgeon 7, Group C)

There was also some discussion about whether the placebo group might receive a local rather than a general anaesthetic. The general view was that whilst this may carry the potential for less risk from harm for the placebo group, differences between the two groups should be minimised as far as possible:

> [Facilitator] So do you think the patients should have identical anaesthesia regardless of which of those two?
>
> From a research point of view, ignore the ethics, but if you want to do this as a pure research thing then yes.
>
> (Surgeon 10, Group B)

There was also some discussion about what should be said to the patient prior to and after their surgery in order to avoid the ethical dilemma of perhaps having to 'lie' to patients about the surgery they had received. A consensus was reached that some sort of standardised procedure would need to be put in place so that the patient would be aware that the doctor was not allowed to disclose details. For example:

> That's what my question is. You don't speak to the patient at all after the operation? Or you read from a same script sheet? Which may, then there is the ethical issue, are you lying to the patient? Or are you not disseminating information to the patient, and I'll have concerns about that as well.
>
> (Surgeon 12, Group C)

> They'll know they may or may not have had it. But you don't have to have that ethical dilemma because before the start you say we won't tell you whether you've had the operation. We will just come up to you and check that things look all right, we won't speak to you in any very useful way, we will be reading from a script. The patients will be expecting that the surgeon will turn up and say 'everything went fine, see you in clinic'.
>
> (Surgeon 4, Group C)

Component 1B – Focus groups with health professionals: the anaesthetists

Methods

An informal discussion session was held with anaesthetists in a regional centre in Scotland (with 45 attendees) to help shape our topic guide. Following this we presented the KORAL study in a plenary session at the BSOA annual meeting, which was held in London, UK, in November 2005. The presentation (attended by approximately 130 anaesthetists) generated lively discussion, and eight anaesthetists from the meeting also contributed to an in-depth focus group session ('Group A') held on the same day. A further focus group ('Group B') with five consultant anaesthetists in a regional centre in the south of England was also held in November 2005.

Focus group content

The focus groups with anaesthetists were facilitated by the lead anaesthetist (BHC) on the KORAL team (MKC assisted at the focus group held at the BSOA annual meeting). The topic guide formulated for use within this focus group is presented in Appendix 3.

As with the surgeon focus groups, the facilitator gave a short presentation (see Appendix 4) that summarised the current research evidence about the effectiveness of arthroscopic lavage (including a description of the process and findings of the trial conducted by Moseley *et al.*[24]); presented the rationale for conducting another placebo-controlled RCT to evaluate the procedure; and explained that the current discussion was being conducted to help assess the acceptability and feasibility of such a trial and help inform the development of the placebo procedure. As before, focus group participants were made aware of the approximate number and associated costs of these procedures undertaken in the UK. The groups were then encouraged to discuss their views about the acceptability of the proposed placebo-controlled trial and design features that would make it more or less acceptable, and what kind of anaesthetic it would be most appropriate to use in the placebo surgery group if the trial went ahead. Throughout the discussion, the facilitator(s) answered questions of clarification and repeated information about the Moseley trial and the current feasibility study as required.

As with the surgeon focus groups, we did not attempt to elicit individuals' attitudes towards the proposed trial in a systematic or quantifiable way, focusing at this stage on identifying the types of consideration that could contribute to their assessments of its acceptability and feasibility.

Analytic procedures

A similar analytic procedure was adopted for the anaesthetist focus groups as for the surgeon focus groups with use of the modified Framework approach.[36]

Findings

The key considerations that featured in discussions about the acceptability of a trial that included a placebo surgery arm included:

- anaesthetists' beliefs about the acceptability of conducting placebo surgery
- views about what would constitute the 'best' anaesthesia for a placebo surgery group
- views about which patients should be deemed eligible for participation.

These are discussed in turn below.

Beliefs about the acceptability of conducting placebo surgery

After the initial presentation, there was general agreement among anaesthetists in both focus groups that the scientific uncertainty about the effectiveness of arthroscopic lavage, together with the large volume, high cost and risk of these procedures, made further research important. For example:

> And the fact is this [Moseley] study has been done. There is a strong suggestion in this study that this therapy is of no benefit. So you come back to the conclusion that it really is very important.
>
> (Anaesthetist 1, Group B)

> I mean first of all is this a real question? Is there equipoise? Is there uncertainty? And there may be. And I think there is a cost. If there are 34,000 people in this country [undergoing arthroscopic lavage], it's a lot of money, and there are risks from them having the anaesthetic and the procedure may not be of benefit. So it's a worthy question …
>
> (Anaesthetist 6, Group A)

The anaesthetists also recognised the significant ethical and practical issues raised by the fact that the proposed trial included a placebo surgery arm. They discussed these extensively, but their opinions varied and no clear consensus was reached about the acceptability of the proposed trial.

The main and obvious concern was the inclusion of a placebo surgery arm, which would require anaesthetists to expose patients to an anaesthetic risk, possibly for no benefit (although as discussed below, some anaesthetists accepted that some patients with osteoarthritis might experience symptom relief after placebo surgery). Key issues of tension related to the uncertainty about the relative benefits and harms of arthroscopic lavage and a placebo version of it, and the competing interests of future patients (and the NHS) and potential trial participants.

Although attitudes towards the proposed trial were not systematically elicited on an individual basis, it was clear that both discussion groups included some people who might be characterised as broadly in favour of it and some who might be characterised as broadly (and in a few cases strongly) opposed to it. It was also possible to identify clear clusters of interlinked reasons associated with these two main stances – although it should be stressed that the participants who were broadly in favour of the trial could nonetheless 'see' that there were significant and legitimate concerns about the proposed placebo arm that would need to be addressed carefully.

Those who spoke in favour of the trial tended to highlight its potential benefits at a population or societal level. They were generally more sceptical about the effectiveness of arthroscopic lavage, and emphasised the possibility that, as currently used in practice, it could be doing harm (or at least that it involved exposing people to the risks of anaesthesia for no benefit), and might represent an unnecessary drain on NHS resources. They were not unconcerned about the individuals who might participate in the placebo arm of the proposed trial (and all participants agreed on the need to minimise anaesthetic risk in this context), but they stressed that it was not clear that those who received arthroscopic lavage would benefit from it, or that those who received placebo surgery would not benefit. Their comments reflected an emphasis on consequentialist ethical reasoning (where the morality of an action is determined by the overall balance of its consequences), although they

recognised that aspects of their professional codes of conduct were in tension with this.

Those who spoke against the trial were perhaps more inclined to think that arthroscopic lavage could be effective, seeing a clearer differentiation between the benefit/harm profiles of the genuine procedure and a placebo version of it. They expressed strong concerns about exposing patients to (any) anaesthetic risk for placebo surgery for research purposes, drawing on principlist (the ethical approach where the principles of respect for autonomy, non-maleficence, beneficence, and justice act as critical directives in bioethical reflection) or deontological (where the rightness or wrongness of an act is determined by the characteristics of the act itself rather than the consequences of it) ethical reasoning and emphasising their professional responsibilities to individual patients.

The key reasons that served to support and to argue against the acceptability and feasibility of a placebo-controlled trial are discussed in more detail below.

(a) Doubts about the effectiveness of arthroscopic lavage and beliefs about the benefits of finding out

As noted above, although there was general agreement among the anaesthetists that it would be desirable to know more about the effectiveness of arthroscopic lavage and to bring clinical research into line with robust research evidence, not all of them were in favour of the proposed trial. Those who were more supportive of the inclusion of a placebo surgery arm tended to be more sceptical about the effectiveness of arthroscopic lavage, and thus more concerned about the potential harmfulness and cost of current practice. They saw the trial as a means of generating knowledge that could potentially prevent significant harm being done in future generations – including harm due to unnecessary anaesthesia. Although they recognised that people who were randomised to the placebo surgery arm of a trial would be exposed to the risks of anaesthesia, they suggested that this could be justified (for patients who consented) because it was a risk to which many people were already being exposed for the sake of a procedure of questionable effectiveness; the effectiveness of the surgery could not be ascertained without doing this, and the risk was outweighed by the scale of the potential benefit:

> … 34,000 people in this per year are having a procedure which has no proof to it. So you're already doing the ladies with the crappy hearts, putting the tourniquets up, giving them the drugs for absolutely no proven evidence … at the moment if there are 34,000 of these procedures being done and we are exposing that number of patients to all the risks of anaesthesia then we need to know the answer.
>
> (Anaesthetist 5, Group A)

> Again it is a question of degree isn't it? … What you are doing is exposing the group of people to risk where there is no potential benefit and that is your placebo group. It is just that you are going to save a whole load of people in the future the risk of an unnecessary procedure, if your hypothesis … You are doing harm to a small number for the benefit of many, you know, a lot of fat people who are going to get unnecessary anaesthetics in the future.
>
> (Anaesthetist 6, Group B)

For some, concerns about the risks of placebo surgery could also be compensated for to some extent by the belief (and evidence from the Moseley trial) that placebo surgery could lead to improvements in patients' symptoms:

> Can I just ask, as soon as you make a skin incision what are you doing to endorphins and things like that? So even though you're saying that this is a placebo, you may actually be achieving some form of treatment.
>
> (Anaesthetist 3, Group A)

> … we know that even the placebo group got some benefit.
>
> (Anaesthetist 4, Group B)

> You could argue that there is an effect in the placebo and so in fact some of those in the control group may well have had benefit, in that they are symptomatically better – and clearly they are.
>
> (Anaesthetist 1, Group B)

For those who thought that patients might derive benefit from placebo surgery, the perceived benefit-to-harm ratios of the placebo intervention and the trial as a whole were improved, and the differences between the benefit-to-harm profiles of genuine arthroscopic lavage and a placebo version of it were relatively small, so concerns about people allocated to the placebo arm of a trial were lessened:

> I don't have any qualms with that [likelihood of a person in the placebo group having anaphylaxis under anaesthetic if there is a low risk of anaphylaxis and lots of people are operated on]. I still believe at the end of the day the placebo effect is very powerful. You are giving three skin incisions to somebody who believes that they had an operation, and a certain percentage of those will be better, will feel symptomatically better … And if we are querying whether the whole surgical procedure is effective anyway, then the people who are having the active surgical procedure with their anaesthetic, who is to say, how are we to say whether they are benefiting or not? That is the whole point of the study.
>
> (Anaesthetist 1, Group B)

(b) Concerns about using placebo surgery and contravening professional ethical codes

The anaesthetists who spoke against the acceptability of a trial involving placebo surgery tended to focus on the interests of prospective individual trial participants. They were more inclined to think that arthroscopic lavage might offer some benefit whilst a placebo procedure would not offer benefit and would still carry a degree of risk. For example:

> You don't know if it's [arthroscopic lavage] not beneficial … Nobody can really say that making a couple of incisions in somebody's skin and not doing anything to them is necessarily beneficial … And you know if I had arthritis in my knee, I would expect to be offered an arthroscopy and there is no way I'd agree to have somebody make two little nicks in my knee under a general anaesthetic!
>
> (Anaesthetist 6, Group A)

They were also more likely to emphasise professional codes of ethics and their obligation to do no harm to individuals:

> As an anaesthetist I would not anaesthetise someone for sham surgery. I just couldn't! I just think it's immoral and unethical … But the Helsinki declaration I mean it's as simple as that, you wouldn't do it.
>
> (Anaesthetist 1, Group A)

The fact that clinical professional guidelines would tend to counsel against the acceptability of a placebo-controlled trial was also acknowledged by some of those who were themselves broadly in favour of the trial on consequentialist grounds:

> Interesting though isn't it because the ethos is the need, your [facilitator's] ethos which I accept is completely logical is the needs of the many outweigh the needs of the few but the GMC [General Medical Council] don't see that do they? The GMC make it very specific in their guidance to us that it is the needs of the individual which is your primary concern.
>
> (Anaesthetist 4, Group B)

This contributed to concerns that there would be significant practical obstacles to running such a trial because it would be difficult to recruit anaesthetists to it:

> The number who will do it this willingly will be very, very small, most of my colleagues would say 'no you're joking' …
>
> (Anaesthetist 6, Group A)

In one focus group, some participants drew on another ethical norm that is strongly emphasised in clinical professional guidelines to question the significance of their own views about the acceptability of the proposed placebo-controlled trial. They suggested that, as long as participating health professionals had attempted to minimise the possible risks to trial participants, it was the securing of informed consent from patients that would be key. For example:

> From the ethical point of view as well, I mean as long as you have been shown to, if you have chosen okay we are going to give both sort of cohorts a general anaesthetic, as long as you have been shown to limit the amount of risk within that, and you have quantified the risk and the patients have signed informed consent then they have consented take on that risk.
>
> (Anaesthetist 3, Group B)

> If the patient is prepared to accept that risk in order to have the operation and they are prepared to enter into the trial on the understanding that they might not have an operation, are we all being a bit precious? Is it really not down to the patient?
>
> (Anaesthetist 4, Group B)

> If the patients agreed to it, then it is acceptable.
>
> (Anaesthetist 2, Group B)

(c) Consideration of alternative study designs

The general consensus that further information about the effectiveness of arthroscopic lavage would be useful, combined with recognition of the ethical concerns raised by the proposal to include a placebo surgery arm in an RCT, led anaesthetists in both discussion groups to consider alternative study designs. They suggested, for example: long-term follow-up studies (retrospective or prospective) to assess outcomes among people who had arthroscopic lavage; comparisons of arthroscopic lavage with no treatment; and conducting the trial among people with osteoarthritis who would be undergoing general anaesthesia for a procedure relating to another condition. In each case, other members of the discussion group pointed out limitations in terms of the robustness of the knowledge that the suggested design would generate.

Consideration of what would constitute the 'best' anaesthesia for a placebo surgery group

Once the groups had debated the acceptability of an RCT comparing arthroscopic lavage with placebo surgery, the facilitator(s) asked them to put their particular opinions about this aside and to assume that the trial was going ahead. They were asked to consider which type of anaesthetic they thought would be most appropriate for the placebo surgery group given both the methodological need to 'mimic' the anaesthetic that would be used in the arthroscopic lavage group and the clinical/ethical need to minimise the risk of harming trial participants.

A few anaesthetists who had argued strongly against the proposed trial expressed some discomfort about identifying the best anaesthetic for a piece of research they did not think should proceed, but in both discussion groups a clear consensus was reached that, if the trial proceeded, participants in both trial arms (the active surgery and the placebo surgery) should receive the same general anaesthetic regimen, and this should be the regimen the individual anaesthetists who participated in the trial would customarily use for a simple arthroscopic procedure. The primary reasons given for this were that: (1) general anaesthesia would usually be used for arthroscopic lavage; (2) the use of general anaesthesia in the placebo surgery group would help ensure the placebo procedure mimicked the active procedure as closely as possible; and (3) general anaesthesia would be the safest option for patients in the placebo group. They rejected the idea of using hypnotic agents (as in the Moseley trial), which might superficially be considered to be 'less risky' than general anaesthesia, because they were not all convinced they would produce adequate anaesthesia for the proposed placebo surgery, and they did not consider them to be safer than general anaesthesia:

> Hasn't the starting point got to be, you should do the same [as for the active surgery group] unless there is a really good reason not to? And if the really good reason is all about risk then you have to show that their [Moseley trial] intervention has less risk than the standard full anaesthetic. I am convinced that that is not the case. So therefore you should do the standard straightforward general anaesthetic.
>
> (Anaesthetist 5, Group B)

> Statistically, [the sedation procedure used by the Moseley trial] is more dangerous than a general anaesthetic.
>
> (Anaesthetist 6, Group A)

The anaesthetists favoured having each anaesthetist who participated in the trial use the form of general anaesthesia that they used regularly, because they had more experience with this and thus would be less likely to make errors when administering it. They acknowledged that this would mean there was some variation across trial centres, but argued that this would not pose significant methodological problems:

> If each centre is randomising then does it matter because as long as each centre is presumably giving anaesthesia to suit that centre and they are randomising so maybe it doesn't make much difference, we could as a department decide how we want to anaesthetise them according to what we have got.
>
> (Anaesthetist 4, Group B)

Patient inclusion criteria

The anaesthetists in both discussion groups discussed which patients should be deemed eligible for participation in the trial, taking into account the potentially competing needs to minimise the risk of harm to participants and to ensure that trial findings would be generalisable to broad patient populations.

The fact that the likelihood of experiencing an adverse event during anaesthesia was higher for

patients with known risk factors for anaesthetic problems supported a general consensus that one of the inclusion criteria for the trial should be having a relatively low grade of risk for general anaesthesia. However, there were differences of opinion around which grading scheme should be used and where the threshold should be set. The American Society of Anaesthesiologists (ASA) grades are in widespread use in practice, and several anaesthetists thought that only patients in the two lowest risk grades, 1 and 2 (i.e. 'normal healthy patients' and 'patients with mild systemic disease' respectively), should be included. Several were keen to further restrict this group to exclude heavier patients (whom they would normally intubate, and who might have problems with reflux) on safety grounds:

> I would be very happy to do the ASA 1 and 2 [on] thin people but the fat people who need a tube, I would just feel a bit more nervous.
> (Anaesthetist 5, Group B)

But the exclusion of (all) patients with an ASA score of 3 or above and the imposition of additional restrictions were seen by others to unduly compromise the generalisability of the study as they might tend to exclude people with more severe arthritis:

> [Facilitator] So could I exclude everyone above ASA 2, for instance? Would that help?
> Yes that would help but then the arthritis is not going to be very severe … you won't get very much arthritis, you're more likely get sports injuries than trauma in that group.
> (Anaesthetist 1, Group A)

> The trouble with that, sorry, if you do introduce those exclusion criteria, then you are going to have the same problem as the Moseley trial, which is generalisability.
> (Anaesthetist 4, Group B)

However, there was no clear consensus about how well or how poorly the distribution of experiences of osteoarthritis would correspond to the distribution of anaesthetic risk along the lines of ASA scores.

Some anaesthetists wondered whether a more specific set of criteria relating to anaesthetic risk could be used instead of the ASA scoring system. They proposed, for example, subdividing the 'broad' group of people who would be classified as ASA grade 3, and excluding people who had experienced severe anaesthetic reactions in the past and those with respiratory problems or heart disease. However, these alternatives could not escape concerns about their implications for the generalisability of the findings of the proposed trial, and in practical terms it was suggested that they would create more work for anaesthetists who might consider participating in the trial:

> ASA I think is frequently used as a score [so] it is going to be very easy to do. I mean it just makes the whole protocol much easier. If you end up with a list of 50 things in it …
> (Anaesthetist 1, Group B)

Component 2 – Focus group and interviews with people with osteoarthritis

Methods

Within the patient stakeholder group we set out to purposively sample patients for inclusion in our study – efforts were made to include a broad range of participants for the interviews, including some participants who may possess special expertise. In doing this, we were thinking about the variables that might influence an individual's contribution, and this was based to a large extent on our practical knowledge of the area.[37] For example, we were keen to speak with people who had osteoarthritis of the knee (and who therefore would potentially be eligible for participating in the proposed trial); both males and females; people who had and who had not undergone previous knee surgery; and people who had been treated in centres that did and did not routinely offer arthroscopic lavage as a treatment option. Members of the support group Arthritis Care were also targeted for inclusion in this stakeholder group, as we anticipated that these people may have a particular interest in and knowledge of the issues that affect people with arthritis.

Thirty-three eligible patients from consultants' lists in a regional centre in Scotland and 26 patients from consultants' lists in a regional centre in central England were approached to take part in focus groups via letters sent out from two consultants; these centres included one that offered lavage relatively routinely and one that did not. The patient sample included both genders and people who had/had not undergone previous surgery for osteoarthritis. Patients were asked to return a form to the research team if they were willing to

be contacted about participating in a focus group discussion (or an interview) for the study.

Ten patients from consultants' lists in the Scottish centre agreed to be interviewed and five from the English centre. All participants gave written consent.

In addition to the interviews, Arthritis Care distributed invitations to Arthritis Care volunteers and members. These were relatively well-informed individuals who provide information and advice to other people with arthritis. They were asked to return a form to the research team if they were willing to be contacted about participating in a focus group discussion for this study after their scheduled monthly meeting. We received seven positive responses and held two focus groups in the north ($n = 3$) and south of Scotland ($n = 4$). All participants gave written consent before participating in the focus groups.

The interviews with people with osteoarthritis of the knee lasted between 30 minutes and 1 hour and both focus groups lasted about 90 minutes each. The topic guide formulated for use within these focus groups is presented in Appendix 5.

Interview and focus group content

Interview participants were sent an information leaflet (see Appendix 6) about the proposed trial in advance of their interview, and focus group participants were given a slide presentation (see Appendix 7) before discussions commenced. The leaflet and slide presentation was developed on the basis of key findings from the focus groups with the health professionals. In particular, a description of the proposed placebo surgery was incorporated that best reflected the consensus that was reached (among health professionals) as how best to minimise potential risk from harm, whilst still ensuring a good mimic of the arthroscopic lavage procedure. Also based on our discussions with the health professionals, the draft information leaflet and slide presentation included details of a third non-surgical management arm.

Participants were initially asked to provide background information about their condition, and their perceptions about arthroscopic lavage were explored. They were then asked to discuss their initial views about the rationale for the proposed trial, including their first thoughts about whether they might be willing to participate in such a trial, and why or why not. The summary of the main issues/dilemmas as perceived by the research team were then introduced to explore any issues not spontaneously suggested and probe them in more detail. Finally, participants were asked to comment on key content features of the draft information leaflet.

Before the focus groups and interviews commenced, the researcher (ZCS) stressed that she and the research team were not wedded to the idea of running the trial, but rather wanted to find out what people thought about it. It was stressed that people were likely to have various reasons for and against participating in trials and that responses were not going to be judged.

Analysis procedures

The interviews and focus group discussion were recorded and transcribed. The transcripts were then analysed thematically using the Framework approach.[36] The research team familiarised themselves with the transcripts and identified sets of themes/subthemes (reflecting both research questions and emerging themes).

Two researchers were involved in the analysis to ensure reliability of interpretation and coding (ZCS and VAE). The primary focus of our analyses was the a priori study objectives. Particular attention was paid to: the types of judgement, belief and attitude (including concern) that people express in relation to the proposed trial; their expressed willingness to participate and factors affecting this; their views on how the precise nature of the simulated procedure and particular features of trial design or delivery might make a proposed trial 'as good as possible' for participants; and their views on what information should be presented and how in the written materials for potential trial participants.

Findings

Sample characteristics

Nine men and 13 women contributed to discussions (15 took part in an individual interview and seven took part in the focus groups). All but one of the participants was aged over 50 years. All but two reported having osteoarthritis either in their knees or in other parts of their body (one participant in one focus group was a carer for her son, who had osteoarthritis of the knee, and one man from the other focus group had received a diagnosis of knee osteoarthritis, but was not himself convinced of this).

Perceptions of arthroscopic lavage/ debridement

The participants reported having tried a range of treatments (including surgery) for their osteoarthritis. Some reported having undergone 'wash out' procedures and debridement in the past. Some also knew of friends and/or family members who had undergone 'wash out' procedures for their osteoarthritis. Participants who had experienced surgery discussed how it had provided some relief from pain in the short term. One woman who received a 'wash out' procedure a few months before being interviewed described how she was continuing to experience considerable relief from pain. Two participants seemed very sceptical about the long-term effectiveness of arthroscopic lavage.

The key considerations that featured in discussions with prospective participants included:

- initial views about/reactions to the proposed trial
- views about their own potential participation in the trial
- views about what information should be presented and how in the written materials for prospective participants.

Views about the rationale for proposed trial

When asked for their initial views about the proposed trial given what they had already read and/or heard from the researcher, it was not uncommon for people to comment about research in 'general' indicating that in their opinion research was necessary for 'progress':

> It's only by doing these sorts of surveys and experiments that you are going to be able to do anything long term isn't it.
>
> (Participant 11)

> … you certainly need studies into all aspects of different ailments and whatever and I think there is a need for it …
>
> (Participant 9)

> You need to find something to help people that's got bad knees … How would they find out about anything if they didn't do trials?
>
> (Participant 17)

Some participants made more specific comments relating to the proposed trial, expressing their views about the need for answers to questions that the trial was intended to answer. For example, one person mentioned the scientific uncertainty surrounding the effectiveness of arthroscopic lavage, and another highlighted the need for research into the long-term effectiveness of such surgical procedures:

> Well, we have got to find out, you know, it has been going on for years and years and no one has ever found a complete answer so things have got to be tried, you know … If you want to advance that is what you have to do.
>
> (Participant 1)

> I certainly think it is worthwhile because at the end of the day … I don't think that people should undergo surgery unless it was having some long-term benefit to them … it should only be done when it is going to have a positive effect and a long lasting effect.
>
> (Participant 2)

Two participants also discussed how, from a research point of view, including a placebo surgical component could be very useful. They explained that this would allow researchers to see if any perceived benefit from arthroscopic lavage was simply the result of a placebo effect. For example:

> … if the Americans [talking about the study by Moseley] are anything to go by, either the lavage is useless or there is a mental stimulus somewhere … I would say it is important to have the placebo in it because if there is a sort of mind set that it does help to heal you, I mean it has been proven over the years that placebos do benefit in certain things, I am not saying all by any means but some of the things can work so it is possible that can work. Maybe that is all you need to do, put everyone under the anaesthetic and then go.
>
> (Participant 1)

> I think a placebo group is a very good idea because it is all about a lot of problems that people have with their performance and their own problems do come from your own mind and if you think something is helping you then you won't feel the pain so I think the placebo group is a very good idea because it can almost fool somebody into thinking they have had a procedure when they haven't and basically prove to some people that you think you are better because you think you have had this procedure but in fact you didn't have any

> treatment done at all so it is all in the mind that you think you have had some sort of procedure if that makes sense.
>
> (Participant 2)

However, in contrast to the above participants who recognised that pain can be subjective, another two participants reported that any pain relief experienced from a given treatment could not simply be a 'placebo effect' given the 'very real' pain of osteoarthritis. These people were keen to point out that people who experience pain from osteoarthritis are not simply 'hypochondriacs'. They questioned the rationale for the placebo component (given that in their opinion it would not result in any perceived improvement in symptoms), and expressed concerns therefore that the study was a waste of resources:

> Now to do this placebo thing which is not of any benefit, I can't see it is because it's not like a psychological pain, if you know what I mean? … some people are going to be given this, they are going to be given a anaesthetic so you need an anaesthetist or whoever else there, it's taking up a bed, it's taking up space in the hospital and nurses time whatever. I know you are only going to be put under and brought back round again but even so I mean our hospital at the moment is in crisis. The placebo thing doesn't make sense.
>
> (Participant 13)

> [Talking about the proposed trial] I hesitate to say this but is it a waste of money? … there are so many people on waiting lists across the country that I think there is enough people there to do a study from … That placebo to me infers that it's all in our minds, to me that's what any placebo infers. If the doctor gives you … when you get placebo tablets off your doctor he's keeping it quiet and saying you are being a hypochondriac but I'll give you this to shut you up. That's what a placebo is to me. [Asked if she thinks others would hold similar or different views] I think people who have had the kind of pain I've had would [be] angry if they were offered a placebo that didn't work.
>
> (Participant 14)

Views about their own potential participation in trial: those who stated they would consider participating

After they were questioned about their initial thoughts on the proposed trial, participants were asked if they would consider taking part in the proposed trial. The majority said that they *would* consider participating, and most gave more than one reason. The reasons related broadly to: (a) an expressed desire to help others; and (b) perceptions about the potential for some form of personal benefit to be gained from participation because of either the interventions being given within the trial (i.e. arthroscopic lavage, placebo surgery) or trial processes (e.g. diagnosis, information). These themes are discussed in more detail below.

(a) An expressed desire to help others

Contributing to furthering medical knowledge and helping future patients was an important consideration for several of those who stated that they would consider participating in the trial. For example:

> I certainly would be willing to give it a go if at the end of the study something definitive came out of it and the management of osteoarthritis is going to be better in future. The treatments are going to be better for people.
>
> (Participant 2)

> I would be more than willing to take part … anything that improves the management and care of osteoarthritis in the future can't be anything but a good thing to be honest.
>
> (Participant 2)

> Well if it is going to help somebody else, yes, I would. The study well you can't do like a study unless somebody like myself would contribute and participate and people be like a guinea pig sort of thing, yes.
>
> (Participant 3)

> I'm not against anybody, I'll let anybody try anything. I always say if I die before I'm 70 I shall donate my body to science! If I think it's going to help anybody else, yes … Yes, I would take part. I would take part in anything. They could do anything to me, anything they wanted! … I am thinking of other people along the line. My mother had MS [multiple sclerosis] for 19 years, they didn't know anything about it for when mama had it … but it would have been great if they could have got a cure and it's just the same as this now … I've had many strokes and I was in hospital and they asked me to take a trial test of things and I've done that and all. If I think any is going to help anybody I'll do it.
>
> (Participant 18)

However, this desire to help others was commonly juxtaposed with expectations of potentially benefiting personally from participation:

> If it means that it is going to help somebody or help me, yes.
>
> (Participant 3)

> It can benefit my kids [who she stated also have osteoarthritis] then fine! If it can benefit me it would be even better!
>
> (Participant 4)

> I'll maybe get some relief from the pain which will help other people as well
>
> (Participant 18)

> I would have it because it's going to help other people … And if I was going to get relief, with just even getting them washed out
>
> (Participant 16)

(b) Perceptions about the potential for some form of personal benefit to be gained from participation

Everyone who stated that they would consider taking part discussed the potential for some form of personal benefit to be gained from participation. For several, the potential for some form of personal benefit to be gained from participation related to perceptions that the interventions being given within the trial might result in an improvement in their symptoms:

> if it worked out that way, that it did help [symptoms] it would be fine, it is a bonus, isn't it, but if it didn't well that is the chance you are taking, you know.
>
> (Participant 1)

> I really can't see many disadvantages in having the procedure done because it is going to because it will or I would say in some cases it will provide them with certainly temporary relief of discomfort in the knee if you are having a washing out because that is the theory behind it at the moment.
>
> (Participant 2)

> Well as I said if I am going to take part in it and if they do, if I'm one of the lucky ones and they manage to do something about it.
>
> (Participant 8)

When participants talked about the 'chance' that taking part might result in an improvement in their symptoms, the majority seemed to be focusing on being randomised to the arthroscopic lavage procedure. In other words, there was a tendency to hope that they would be allocated to arthroscopic lavage rather than placebo and that the intervention would/might be beneficial. For example:

> It doesn't concern me but it doesn't, you have to be, how do I put it, its a trial and like anything else you get the lucky one that gets the actual procedure and if you are not the lucky one you get the placebo but …
>
> (Participant 3)

> [asked by facilitator if not knowing what she would get would affect her decision to take part] I think I would still go through with it but if I discovered that I wasn't getting help, you know that my knee was still as bad I would want to go through the wash out to get relief.
>
> (Participant 19)

However, only one participant discussed how being randomised to the placebo might still result in symptom improvement:

> … if it helped, even if it was only mentally, you know, it would probably be a good thing … Well I mean obviously with the results they [Moseley trial] came up with, they got just as good a result on the placebo so obviously it is a mental thing rather than a physical thing on that score you know, so possibly it would help you, you don't know, so you maybe mentally think yourself better, I mean it has been proven hasn't it, that the mind is part of the body, if you know what I mean it runs the body.
>
> (Participant 1)

For some other participants, the potential for some form of personal benefit to be gained related to trial processes, such as getting an 'official' diagnosis:

> I would find out if I had it in my knees or if it was just wear and tear – that would help.
>
> (Participant 3)

> Now I don't know that I should benefit from it at all. The only thing I should be going for to fathom out what this is, what is wrong with my knee … Well you can't get no further forward at all with this lot around here but I will quite willingly have a go like you know.
>
> (Participant 15)

For another, this related to the potential to become more informed about the most effective ways to manage osteoarthritis:

> I would know or that I would hope to sort of at the end of the study to be aware of the best ways of, what would be the best management of my problem would be. I would know that well either arthroscopic lavage was a possibility if my knee did get any worse if it was seen to be a worthwhile procedure or whether it was just going to be a case of effective management myself. My personal view is that anybody taking part in the study would get some benefit from it because going through like a study like that they are going to understand what they need to do, what the doctors are seeking to achieve so.
>
> (Participant 2)

Potential to be harmed by the interventions

When discussing their reasons for possibly taking part in the proposed trial, participants focused on the 'chance' that the interventions being given in the trial might improve their symptoms without a corresponding focus on the 'chance' that participation might result in some harm. Instead, participants tended to argue that their taking part (and being randomised to either lavage or placebo) would likely not cause any deterioration in their current symptoms. In other words they seemed to think that 'at worst' participation would result in no harm. For example:

> I would be willing to take part in the study to be honest, I will, I am sceptical about whether surgery helps, I don't think it would do you any harm … I don't think my knee could get much worse to be perfectly honest.
>
> (Participant 2)

> The only possible disadvantage was if it made anything worse really. I would expect it to get better, to improve things, but if it didn't I wouldn't really expect … for arguments sake if it was the placebo procedure … That I wouldn't expect things to be any worse after that. I would expect it to be the same as previously you know.
>
> (Participant 11)

Only one participant, who stated that she would consider taking part, mentioned the possibility (which she considered unlikely) that her participation might lead to a worsening of her pain symptoms. She associated this possibility with arthroscopic lavage, not placebo surgery:

> Well, the only disadvantage would be if, not that it wouldn't work, but that it made you worse, but I can nae see that. But maybe it would, maybe I don't know enough about it. But that would be the only disadvantage, maybe if you came out and thought 'oh well, aye, its OK' and then maybe the next month you're in more pain than you were.
>
> (Participant 4)

However, she pointed out that she tends not to focus on what might go wrong:

> But do you think with any surgery, they ever really know that its going to work? I'll go back to my [previous foot surgery], the amount of people that were saying 'Oh I wouldn't get that done, such and such is crippled and has never walked' you know what I mean … the scare stories you get beforehand and the ones you get after, you've just got to ignore them and maybe some people cannot.
>
> (Participant 4)

Participants who stated that they would consider taking part did acknowledge that their participation *might* involve some harm: (a) from receiving the arthroscopic lavage, (b) from the placebo procedure, and (c) from the general anaesthetic procedure, with some stating that it 'would worry you a little bit'. However, these harms tended to be downplayed in discussions in comparison with the potential benefits that might be gained. For example:

(a) Harm from arthroscopic lavage procedure:

> There's a very slight risk, but chance also the symptoms would be held at bay, and then, you know, for a few more years I could be enjoying my bike rides and my walks … please, God, and I might be able to start running again.
>
> (Participant 10)

(b) Harm from placebo surgery:

> … that would worry you a little bit obviously, you know, you go in there and somebody cuts your knee for really no reason you know, that would sort of bother you but if it helped …
>
> (Participant 1)

> Well, I've got a lot of marks, marks on my face and my body so, I mean not tattoos and that, but scars and that … So another couple of scars wouldn't matter!
>
> (Participant 6)

(c) Harm from general anaesthetic:

> I mean, if you are getting an anaesthetic there is always, albeit I think it is quite small, risk of complications with anaesthesia but I mean that is, I would say unless there are figures I am unaware of, there is very, there is, there can be problems but they are very few and far between and if the right patients are selected then I don't think there would be any problems.
>
> (Participant 2)

> The only down side is the only risk is basically the anaesthetic procedures that I can see … I think the only down side to the placebo aspects of it are the slight risks of the anaesthetic. I mean you are not going to get any after effects and if the anaesthetics procedure go okay, then I can't see any disadvantages to that.
>
> (Participant 2)

However, although not apparently overly concerned with any risks specifically associated with the surgery or anaesthesia, one of these participants did mention being concerned about possibly acquiring a hospital-associated infection whilst in hospital:

> The only thing is that bothers me about going into a hospital and having a nick in your leg somewhere or other, I've got two friends who went in to have knees done and they both got this MRSA [methicillin-resistant *Staphylococcus aureus*] and they are both on sticks completely now and they've been told it will probably get gradually worse.
>
> (Participant 15)

Several of the participants who downplayed the significance of any potential harms for their own participation in the proposed trial nevertheless acknowledged that other prospective patients, depending on individual circumstances, might be more concerned about potential harms from the interventions being given in the trial (both lavage and placebo groups). For example:

> I mean maybe I am a bit laid back when it comes to that [the possibility of being randomised to placebo surgery], it doesn't bother me but I know a lot of people would hesitate to have surgery just for the sake of surgery …
>
> (Participant 1)

> [discussing risk associated with general anaesthesia] It is a thought that one, you know, that would probably be a stumbling block for both groups [surgery and placebo groups] … you would cut your number of people willing to do it by the fact that you do that … no one wants to put themselves under an anaesthetic for nothing basically, they would have to weigh the advantages against the disadvantages in their own specific case … if they are really bad they would be going for it in the hope that they would benefit.
>
> (Participant 1)

> Definitely some people would be scared, I'm thinking of my mother and my sister, they, they certainly wouldn't take part … Firstly, they hate being in hospital … some people they depend on their job and they probably would be reluctant to take time off work, although it's just a few days.
>
> (Participant 10)

Potential to be inconvenienced by participating

Some of those who had stated that they would consider participating did, however, recognise that participation might be inconvenient:

> It's not even that, it disrupts what they're doing within the family. You know the likes of you watching your grand bairns [grandchildren]. It could disrupt you for a while.
>
> (Participant 17)

Some thought that the inconvenience would be greatest for those randomised to the proposed third arm of the trial, management without surgery, e.g. physiotherapy. Several were of the opinion that those randomised to the third arm would be more inconvenienced than those randomised to the other groups, particularly if they were required to attend regular physiotherapy appointments:

> To go up and get appointments and things like that, maybe twice a week or something like that, me personally I've not got enough time in my life to do this once or twice a week.
>
> (Participant 4)

> So, if it's younger people that work … as I said, I work Monday, Tuesday, Thursday, Friday, but a Wednesday is the day I take my mother

> out so really if I get a chance of a couple of hours to myself on a Wednesday I take it and I don't want to be going up to the hospital for physiotherapy to be quite honest.
>
> (Participant 4)

One participant who indicated that they would prefer to be allocated to the arthroscopic lavage group also questioned whether physiotherapy would personally benefit them:

> I'd like to think that I would be in the lavage group but if I am not, as I say so be it. … if it was physio, if it was anything like what I experienced previously I don't feel that I got any real benefit from that.
>
> (Participant 11)

Whilst another expressed some reservations about being potentially asked to take tablets if randomised to the third arm:

> the only reservation I have got against it is that it seems to me there are three options, that one of the options was taking tablets. Well I am actually one of the world's worst for taking tablets. I am very fortunate that I come from good stock because I don't need to take tablets.
>
> (Participant 15)

Views about their own potential participation in trial: those who stated they would not participate

Although most of the participants interviewed stated that they would consider taking part for the reasons outlined in the sections above, a minority expressed reluctance. Despite expressing a desire to help other people by becoming involved in research, perceptions of uncertainty regarding the potential to benefit from the interventions being given within the trial as well as the potential to be harmed by the interventions was a concern.

Unlike the majority of the participants for whom the potential to personally benefit from the interventions was enough to make them consider participating, for this group of participants the lack of a 'guarantee' of personal benefit seemed to dissuade them:

> It's no use me taking part in anything that isn't guaranteed to help me … The only thing that is stopping me from definitely saying yes I'll take part is … it won't do me any good at the end of it, it's the uncertainty. If I knew that it would do me good then yes I would do it because I'm a great believer in helping other people in years to come … as I say if it was certain that it would help then yes I'd say I would go ahead with it but the uncertainty, no.
>
> (Participant 12)

> If I was informed then that I had had the placebo and I realised that I had still got the pain I would be so furious … So angry. I'm afraid that whoever was involved their feet wouldn't touch the ground!
>
> (Participant 14)

For them, the potential for some harm to result from the interventions also appeared to be a deterrent:

> If I could do it without harming me then I would take part …
>
> (Participant 12)

> One thing that really did concern me was the fact that it would have to be a general anaesthetic even for the placebo. I mean I don't want to have an anaesthetic for nothing … Well I just think it's risky anyway. It's not something that anyone will want to put themselves through for no reason.
>
> (Participant 13)

Despite expressing reservations about taking part in the trial, like those who stated that they would consider participating, these people nevertheless made positive statements about research and expressed some 'regret' at feeling unable to take part:

> … I've got a lot of things wrong with me but if it benefit other people and it didn't harm myself then yes I would … If I knew that it would do me good then yes I would do it because I'm a great believer in helping other people in years to come.
>
> (Participant 12)

> I think the advantages obviously would be helping the people who have helped me over the years. I was saying to my husband I'll do anything. I fill in forms regularly for doing research at the hospital now. Those are the advantages, helping other people to gain something from it I suppose in the years to come or whenever … giving something back … I can't agree to do it and I'm really sorry about that because like I say I would like to help, I

> would like to give something back for all that's been done for me but I can't do that.
>
> (Participant 13)

Views about what information should be presented (and how) in the written materials for potential trial participants

All the participants reported that they had understood the information that was presented in the information leaflet (that was sent to them in advance of the interview), and that they understood what was being proposed. Most participants made general comments relating to the information being 'easy to understand' and 'clear'. For example:

> Aye, it's quite explicit, it's telling you, it's the dummy [referring to placebo].
>
> (Participant 18)

> … or the real thing [referring to lavage].
>
> (Participant 16)

> [Showed leaflet to wife (nurse)] I think she knew exactly what was being set out here I think.
>
> (Participant 9)

> I think the information that is on here for somebody that would take part is excellent. It says it all it is very good at saying just exactly what they would want to know and the questions have been answered, in my opinion.
>
> (Participant 22)

However, some of the participants' comments during the interviews suggested they had not fully appreciated all the key points. This is illustrated by the following quotes which suggest that some participants made assumptions about arthroscopic lavage being an effective treatment:

> Could I keep this to show my sister [draft of information leaflet]? It's not going ahead. Yes, it's just to show her that she could maybe ask for that.
>
> (Participant 3)

> I had it in my knees I would certainly go for it … I think I would still go through with it but if I discovered that I wasn't getting help [if allocated to the placebo group], you know that my knee was still as bad I would want to go through the wash out to get relief.
>
> (Participant 19)

Others perceived that treatment assignment would not necessarily be random and that health professionals and/or patients themselves could have a say:

> Would that not depend on how bad, you know, when you get the x-ray and everything. How bad it looked from inside? No?
>
> (Participant 4)

> She [pointing to facilitator in focus group] could put down next to the name, this lady would like wash out!
>
> (Participant 16)

> If people thought they could sort it without the operation they would go for that [physiotherapy].
>
> (Participant 4)

Only two participants made specific suggestions about how they thought the information leaflet could be improved. These suggestions related to providing more information to prospective participants about what is meant by placebo surgery (and how many operations a participant would expect to receive within the trial) and making it clear that they would receive a general anaesthetic. A suggestion was also made that the information leaflet should include more detail of the nature of any proposed follow-up appointments. For example:

> Possibly an explanation, I understand what a placebo is but an explanation about the word placebo quite a lot of the people wouldn't understand what a placebo is, I think that is about the only thing if you could explain clearly that nothing will be done other than that, the placebo … I am not saying I am brilliant but the word placebo is not in common use it is only in the sort of, medical circles.
>
> (Participant 1)

> I mean I don't know the only other thing that I did wonder was would there be more than one surgery or one pretend surgery if you like, during the course of the 2 years.
>
> (Participant 2)

> [suggesting that the words general anaesthetic are highlighted] [so that] the eye is drawn to it … you don't want people turning up for the 'oh general anaesthetic, oh no no not for me! I thought it was just, you know!'
>
> (Participant 1)

> You could put in there is maybe more information about what the follow-ups would be and stuff like that to be honest aye what the follow-up sort of appointments would entail.
>
> (Participant 2)

Component 3 – Interviews with chairpersons of the UK Multicentre Research Ethics Committees

Methods

Full MREC approval was received for this phase of the study. To preserve their independence with regard to any future ethics decisions about KORAL, the MREC that approved this part of the study was excluded from the interviews of chairpersons of research ethics committees. Twelve ethics committee chairpersons were invited by letter to take part in a telephone interview. Of these, six replied and agreed to be interviewed. Interviews lasted between 45 and 90 minutes.

Interview content

The interviews with MREC chairpersons were conducted by one researcher on the KORAL team (ZCS). The topic guide formulated for use within these interviews is presented in Appendix 8. All interviewees received written information about the proposed trial before the interviews took place. The researcher also briefly summarised the proposed trial at the start of the interview, providing an overview of key findings from the previous discussions with other stakeholder groups. The interviewees offered their personal opinions on various aspects proposed but also attempted to reflect broadly what their committee would want to know.

The interviewees were encouraged to discuss their views about the acceptability of the proposed placebo-controlled trial, and the criteria that the trial would need to satisfy to be considered ethically acceptable. Throughout the discussion, the interviewer answered questions of clarification and provided/repeated information about the Moseley trial and the findings of the current feasibility study as required.

Analytic procedures

The interviews were recorded, transcribed and analysed thematically using a modified Framework approach.[36] Following initial familiarisation with the transcripts, the data were coded according to a series of broad themes that reflected both the main research questions and key issues that emerged in discussions. Charts were created to summarise the data relating to each broad theme, and these were used to develop a characterisation of the range of beliefs and opinions expressed by the MREC chairpersons on issues salient to the acceptability of the proposed placebo-controlled trial.

Findings

The key considerations that featured in discussions about the acceptability of a trial that included a placebo surgery arm included:

- the chairpersons' perceptions of how their committees would view the proposal
- the design/methodological criteria that the proposed trial would need to satisfy to be considered ethically acceptable
- the nature of information that should be provided to prospective participants.

These are discussed in turn below.

Likely ethics committee response to the proposal

Views were broadly consistent with regard to how the chairpersons thought their committees would view our proposal. The chairpersons did not think that their committees would necessarily immediately dismiss the proposal on the basis that researchers were planning to incorporate placebo surgery. Rather, they thought they would focus instead on how researchers had attempted to justify their proposed design. The fact that our research team had accessed and considered the views of key stakeholders was considered favourably. For example:

> I like that. That will get you lots of brownie points in that you've asked the participants, in that you have involved the participants in finding out what they want to know.
>
> (MREC 6)

All the MREC chairpersons agreed that the scientific uncertainty about the effectiveness of arthroscopic lavage, together with the large volume, high cost and risk of these procedures, made further research important. For example:

> [facilitator pointing out that because of the uncertainty of effectiveness of arthroscopic lavage, one could argue that patients out with the trial having lavage face potential of risks for no benefit] Yes, I do yes, that is a very good argument for doing it. One in fact, one of the

> best arguments for doing it … Yes, the point, the reason that why it is a good argument is that as you say, we might be doing thousands and thousand of general anaesthetics for a procedure which is absolutely useless.
>
> (MREC 2)

> … long term if you are carrying on it is unethical to carry on cutting open peoples' knees … when it may or may not work and shoving stuff into their knees when it may or may not work.
>
> (MREC 4)

> I can't speak for the committee, but I know how people to a large extent think and I think that if there is a treatment that you are doing with all the risks inherent in it and you don't know whether its any good or not you have a duty to find out whether there is evidence for doing it. So there is an impetus to do it.
>
> (MREC 6)

The chairpersons also acknowledged that there were 'good' ethical and methodological arguments for incorporating a placebo component into the proposed design, including for example, that current uncertainty of scientific benefit meant any potential risks and benefits were arguably equivalent between the groups. Furthermore, there was also an argument for placebo surgery given that pain was to be an outcome. For example:

> … what we would probably say is that we would not be running away from saying it is a 'no-go' [to do] a sham surgical procedure, we look at everything on its merits … I can see no reason why in sort of in principle, I mean that it should not go ahead and I think it is probably very important that it does … one cannot say that they [placebo group] are getting lower than the standard of care because we don't even know whether that [arthroscopic lavage] works … I think in a sense they are all, they are a whole equal pool if you like at the start because one needs to know whether we should be doing this to them … at the moment we don't know if it is even effective or not one cannot say that therefore we know that it [arthroscopic lavage] is an advantage because we don't know whether it works or not so there are probably equal points for these people as well … and also because of having self-reported patient outcome one sees the need for a placebo group.
>
> (MREC 1)

However, the chairpersons argued that whilst, in principle, the trial would not necessarily be dismissed, particularly if good justification for aspects of the study design were provided by the research team, members of ethics committees would tend to focus on the interests of prospective trial participants (particularly those in the placebo group), and the fact that they would be exposed to risk (for no personal benefit) would be particularly problematic and would result in a 'rough journey' getting through a committee:

> I fully appreciate that, thousands of them could be done and an awful lot of time and money could be saved if you don't need to do them. I couldn't agree more but that is obviously your point but again that doesn't get over the problem of anaesthesia, does it?
>
> (MREC 2)

> And without going into too much background I would have to say that I would have to think extremely laterally to envisage that this would get through without a very rough journey on the way … We have one committee in particular which anything placebo can solve is evaluated with a fine tooth comb and there we're talking little white tablets … The prospect of using a surgical approach I think raises the stakes enormously.
>
> (MREC 3)

> There does seem to be, there really is an issue about participating in something that you are not immediately going to benefit from … and carrying some risk which is I think the anaesthetists would say is unquantifiable.
>
> (MREC 4)

> Whereas most placebos are no drug, or no procedure, no risk this does carry a risk because of other things that you're doing. Clearly if we're going to protect a patient we need to look at the risk or the risk/benefit ratio. The benefit is not obvious, because you are really seeing whether you have a problem with the existing treatment.
>
> (MREC 6)

There was also acknowledgement that there would likely never be consensus among ethics committee members about the acceptability of the proposed trial, and that a decision one way or another would probably be heavily influenced by particular members with strong views:

> I imagine what usually happens in these sort of things which are highly controversial is that even if you talk to medical ethicists, you would never get a consensus of an answer, and you will get some that say it is okay and some that say it is not.
>
> (MREC 2)

> My experience with something like this, which is quite vast actually, is that you would have different views from different people and coming from different directions. On a research ethics committee the slightly ironic thing is that you don't always have people who have got a vast number of research experience … Now the way discussions usually go is that they are very open and occasionally opinionated and you do get views as I said coming from different directions but if you find any two of those gelling then usually that is enough to carry a decision or carry the argument in one direction or the other … you often get a very strong voice from, not an interested party, but a knowledgeable party on what's going on and a committee can be swayed very, very easily towards one decision or another … And research might not actually come into it.
>
> (MREC 3)

Design/methodological criteria that a proposed trial would need to satisfy to be considered ethically acceptable

Several of the interviewees argued that because there is a justification for the proposed research, ethics committee members tend to focus on the potential risks participants in the placebo group might face. In similarity to some of the findings reported from the health professional focus groups, it was reported that committee members would be inclined to think that a placebo procedure would not carry any benefit to the individual (but would carry a degree of risk):

> Obviously the risks to them first of all … I would think that in conclusion is probably the general anaesthesia that will cause ethics committees the most problems because then they will say now is this really too much of a risk to be giving somebody a general anaesthetic for nothing … I can see everybody say, oh oh no way not general anaesthetics.
>
> (MREC 1)

Interviewees also stated that committees would consider whether adequate indemnity/compensation procedures were in place to support both patients and the clinicians who treated them, should someone be seriously harmed by participation in the trial. They tended to focus on those receiving placebo, rather than arthroscopic lavage, despite their own suggestions that participants are potentially being exposed to the same risk–benefit ratios:

> The other thing which I would think about, is what would happen to whom if there was shall we say a disaster, a fatality in one of the sham procedures … I would certainly want you to have thought it through. Because, you know the worst-case scenario, you are going to anaesthetise a fit, healthy, 30 year woman who then dies on the table under the anaesthetic you know, they, God she has got two young children and this that and the other and we find out it is the placebo and all the rest of it or the legal implications of it could be huge, couldn't they?
>
> (MREC 2)

> And that brings me back to the vulnerability of the anaesthetist if everything goes pear shaped … Yes, and I would think I would think it could even be a good idea to have a consent form for the anaesthetist … That would be a good idea because that would ensure that the anaesthetists are acutely aware of everything and that he is officially sanctioned to do it.
>
> (MREC 2)

> If you cause harm are you indemnified or the folk doing it under the non-negligent or the negligent provision? The trust will indemnify you for negligent harm, universities are constrained to indemnified for non-negligent harm, but [what] happens when it's deliberate harm? In other words you're doing something, you're damaging the patient for no benefit deliberately … The anaesthetist would probably be alright that would be either negligent because they are not causing harm deliberately so they are probably covered by NHS indemnity but the surgeon who actually causes harm by inflicting a wound which was not part of any treatment is that actually non-negligent or is that deliberate?
>
> (MREC 6)

Nature of placebo

The chairpersons were asked to give their opinions about the nature of the placebo that was being proposed. It was made clear that details of what the placebo might consist of had already been

extensively discussed with orthopaedic surgeons and anaesthetists (from the point of view of attempting to maximise the mimic but also to ensure that any risks were minimised). Although the interviewees had expressed some concern about how the trial would be received by an MREC (for reasons discussed above), their opinions about how best to minimise risks to participants (and therefore standing a better chance of being viewed favourably by members of an MREC) were broadly consistent with those expressed by the health professionals. For example, the proposed three superficial cuts that would just pierce the epidermis (with no penetration of the knee capsule) was regarded as acceptable, as was the plan not to insert a scope into the incisions:

> … actually doing little cuts? No, I don't. I don't have a lot of trouble with that. I suppose you could get round that by bandaging the knee can't you?
>
> (MREC 2)

> The brief skin incisions I think is acceptable but anything further than that probably wouldn't be.
>
> (MREC 1)

There was general agreement that participating surgeons should be allowed to perform additional debridement procedures if they believed that they were necessary for an individual patient. For example:

> If you actually did insert an arthroscope and take it out again then once you have actually seen what the knee was like inside, you would probably be ethically bound to do something about it if it needs it. So really anything that actually meant that you actually invade with an arthroscope it couldn't really be ethical if you actually then do nothing.
>
> (MREC 1)

The chairpersons did express concern about the need to give placebo patients a general anaesthetic, but accepted that we had explored possible alternatives with anaesthetists and that from a risk minimisation point of view they were probably better performing a familiar procedure:

> [after interviewer summarises findings from focus groups] Yes, well I would agree with that. I can speak to you with a degree of authority on that.
>
> (MREC 2)

Also in similarity to the views expressed within our focus groups with health professionals, MREC interviewees highlighted the need to minimise any specific anaesthetic risk by paying careful attention to the patient inclusion/exclusion criteria, with one interviewee suggesting that an 'independent' anaesthetist should be involved in the selection of suitable patients:

> I think the inclusion and exclusion criteria would have to be very carefully designed if these people are going to be given general anaesthetic … that would be quite a major ethical point.
>
> (MREC 1)

> I would think that people would need to be reviewed … by either, I'm thinking laterally you understand, whether even an independent, whether people having, considering entering the study should have an independent anaesthetic assessment … I mean I think that might weigh with me. I mean I would want to make sure you know I think I would feel happier if an independent anaesthetist not connected with the study was asked quite simply to review the suitability of the patient for an anaesthetic.
>
> (MREC 4)

Other trial design issues

The focus of the discussions with the MREC chairpersons tended to be less about specific methodological aspects of the trial and more about the key ethical dilemmas involved (it was highlighted that methodological issues should have already been scrutinised at the funding stage):

> They will look at the science obviously at that stage and make sure that what you saying you are doing you are powered to do and you are going to be able to do it. If that has been done then the research ethics committee can normally say 'good that has been done we don't have to look at that again'.
>
> (MREC 1)

However, as one chairperson indicated, there is an inevitable overlap between methodological and ethical issues, and so certain general trial design issues (that could have ethical implications for any trial) were highlighted as being important for ethics committees to focus on. For example, the need for an interim analysis to monitor trial results; different approaches to recruitment (and how this might affect recruitment rates); and

the role/motivation of the postoperative assessor (i.e. are they likely to be involved in the patient's care or simply interested in research outcomes). Interviewees stated that committee members do not always have the methodological expertise required to judge the appropriateness of certain aspects of trial design and so therefore frequently rely on the justifications provided by the research team (and need to have confidence in the research team's competence in being able decide the most appropriate approach). These justifications are particularly important when they involve exposing prospective participants to risk from harm:

> … and I mean the other question which I would ask would be is that is there any other way of tackling the equipoise, is this the only way you have available, to which I am sure … I would also, let me put another … I'd want a very robust justification for tackling the equipoise in this rather risky, in this potentially risky way. I think any self-respecting committee that is the question they would ask. I would certainly be weighed by what risks our anaesthetic colleagues thought fair. I mean you've got to, you can't negate the risk … If the study is going ahead, there is a risk, you can't negate it … I think I'd want evidence that the risks had been fully considered and minimised … I've just you know and my experience is you know are anaesthetists are a very ethical lot indeed … And they serve as a very useful counterbalance to the surgeons … I can see the surgeons are faced with people in awful, intractable pain and they want to do something about it.
>
> (MREC 4)

> It would be a very important issue that we would want to look at in detail and of course having advice already from anaesthetists is very important for research ethics committees … To know what the professions would have to be dealing with this, considered to be the relative risks of a general anaesthetic.
>
> (MREC 1)

The information that should be provided to prospective participants

All the chairpersons argued that (assuming researchers had successfully convinced them that the potential for personal risk of harm had been minimised) a very important consideration for the committee members would be the nature and extent of information given to prospective trial participants, and the consensus was that researchers should be as 'transparent' as possible. One chairperson stated that this focus was because, ultimately, ethics committees exist to protect the rights of patients – they need to be assured that prospective participants know the risks involved and that consent will be truly 'informed'.

For example:

> I am a great believer in the fact that if consent is properly informed then you can do just about anything you want to anyone … Well you would have to have an absolutely impeccable patient information sheet, you would have to make sure that the patients had probably a reasonably amount of time, shall we say a week or 10 days to think about it and so I would say more than 24 hours and they should be encouraged to discuss it with other people, their doctor, their family, their friends and things like that … it is only when …you have got a very open patient information sheet … then you know, I don't think you would have a problem …you wouldn't have a problem with MREC.
>
> (MREC 2)

> I suppose my view is that it would for me it would stand or fall on the quality of the patient information, and that if the patients knew and accepted the risks then for what I would guess are the lowest risks attached to an anaesthetic, I might be prepared to suggest the Committee take a favourable view of it … Now I think sometimes we represent the public in a more important way than user groups … Well you see it is our most common reason for bouncing a study is poor patient or participant information … But I mean I also don't think we can be too paternalistic you know we, one of the things we have to do is use our commonsense and use our expertise and also we do have also have to also say what's reasonable.
>
> (MREC 4)

However, there was also acknowledgement that ensuring informed consent had been obtained from participants is not always a straightforward process of providing information because of issues relating to the public's understanding of science (which is sometimes exacerbated further if a trial includes older patients). In particular, the tendency for trial participants to believe that their participation will result in personal benefit was

mentioned, as was their understanding of concepts such as randomisation:

> I think what I would comment is the tried old phrase that the good old therapeutic misconception, is the minute you ask some people to go into a trial whenever you tell them they are not going to get any treatment or they could even get worse, they seem to still believe that they will get some benefit and in something like this where you know we really do not know what benefits they will get and they may get none what so ever and they will still have to go through 2 years of follow-ups.
>
> (MREC 1)

> I mean we have conducted surveys ourselves with people coming out of their interview in which they have signed up for a randomised trial and you say, you do understand what it means don't you and they say, yes, he explained it all to me, and we say well you do understand that you have a one in two chance, oh no I know I am not going to get the drugs. I have already and I know the doctor and she told me that but I know I am not getting it really and I think, this is the awful problem, the younger generation come up through schools now and have actually done proper controlled sort of… The older generation… by 75 year olds still wishing to please their doctor and will virtually agree to anything if they think it is actually helping other people… they may be gritting their teeth and carrying on with pain rather than come out of your trial.
>
> (MREC 1)

> People frequently sometimes take part in a study thinking they have been quote, unquote 'given a new treatment'.
>
> (MREC 4)

Discussing exactly what and how prospective trial participants should be informed about the proposed study, the chairpersons focused on three broad areas: (a) the potential 'risks' to the individual from participating; (b) the potential 'benefits' to the individual from participating; and (c) their 'rights' should they decide to participate. Again, despite suggestions that participants are potentially being exposed to similar risk/benefit ratios, the emphasis was on making sure that the potential risks from receiving the placebo surgery were made particularly apparent. These are discussed in turn below.

(a) The potential 'risks' to participants from participating

All the chairpersons stated that prospective participants should be clearly told that participation might mean receiving placebo surgery (that would also entail having a general anaesthetic):

> That is quite common. What I think my MREC would probably say is that there should be a special paragraph perhaps outlined in highlighted words or perhaps boxed in with a black border, it is I think it is very unusual thing that is happening and it is important for them to realise that they are having an anaesthetic under which no treatment or any other procedure whatsoever will be done.
>
> (MREC 2)

> Normally we say well there are some things that don't need to be spelt out but I think that [general anaesthetic] would need to spelt out very clearly and very fully.
>
> (MREC 4)

The extent of any potential risk from the proposed placebo 'incisions' as well as from general anaesthesia was also considered important to highlight and it was discussed that how information is presented can also affect interpretation and ultimately recruitment:

> …additional slightly higher than minimal risk of having three incisions… they will have obviously have to have explained to them the standard problems of a general anaesthetic so that they do agree to that.
>
> (MREC 1)

> …and obviously make it very clear, I suppose as well, thinking of patient information, that there would be, if they were in the placebo group they would be getting a general anaesthetic and obviously explaining the risks of, the potential risks of the general anaesthetic… there is transparent and more murkier ways of doing that so you would say that any general anaesthetic will carry potential risks, is one way of saying it which is slightly different to saying we can assure you that the risks of having a general anaesthetic are extremely small… Now the words sound very similar but the flavour of one is to encourage people to take part, in the flavour of the other, it is laying it on the line and making sure

> people understand exactly what they may be letting themselves in for.
>
> (MREC 3)

Other potential inconveniences involved in participating, such as hospital visits and time off work, were also highlighted as being important information.

(b) The potential 'benefits' to participants from participating

No chairperson argued that potential participants should be told about how their individual participation might help other people with osteoarthritis. However, one chairperson stated that prospective participants should know the potential personal benefits from taking part (but the focus here was on being randomised to the non-surgical arm rather than one of the surgical arms) by getting access to extra 'care':

> On the other hand of course, that extra attention and visits I would have said may be quite valuable to them so your third arm who doesn't get any sham procedure at all but gets that probable care if you like, therefore will be, it will be very important to explain to those people that they are actually, they are potentially getting a possible benefit because they are going to have that attention but of course there is no way that anybody is going to guarantee that they are going to be actually better in the result of it, as long as that is actually very well explained to them.
>
> (MREC 1)

Another indicated that it would not be unethical to suggest in the information leaflet that patients might receive personal benefit if they were randomised to the arthroscopic lavage arm, despite the lack of scientific evidence of effectiveness:

> If you had a surgeon was carrying out lavage as a standard procedure on a very regular basis then you would be justified in saying your surgeon would be either Mr Price or Mr Jones who carries out 200 of these operations every year and the evidence suggests that it is one standard approach and the likelihood of success is and they would be able to give it and the weight of improvement and the weight of a successful outcome and also say that it may be unpredictable and that there may actually be no benefit of this procedure either.
>
> (MREC 3)

However, the same interviewee was adamant that in no way should we state any potential benefit from receiving the placebo:

> I think if that was made clear with language like, you must appreciate that following this general anaesthetic and mock surgical procedure, if you, if that's what you get you will not benefit at all as far as osteoarthritis of the knee is concerned and that would have to be done honestly and really upfront. And you can't say it is unlikely that, this presumably with superficial cuts above the knee which is all it is would be an absolute, this will not be a benefit to you at all
>
> [facilitator] What was interesting,… they might get some benefit but it might just be from actually thinking that they've had this surgery, if you see what I mean.
>
> [interviewee] Which you can't … can't imply, if you did that you would be strung up by painful bits and … you cannot assume a placebo effect.
>
> (MREC 3)

(c) The 'rights' of participants

In addition to the need to provide prospective participants with clear information about the potential risks and benefits involved in participating, MREC interviewees also talked in detail about the need to provide information about their 'rights' as participants. A range of issues were highlighted as being important, and several of the chairpersons argued that participants should be made aware about the following:

The ease with which patients can access the 'active' treatment (i.e. lavage) out-with the study:

> Whether there are options if they decide not to go into the trial because there will be a situation of course, I don't know what the waiting list is in NHS hospitals for arthroscopic lavage. If they actually are able or likely to get a 30% possibility of getting arthroscopic lavage straightaway if they go into the trial and they are told they will have to wait 18 months if they don't go into the trial it may be slightly coercive … if they were told they can have arthroscopic lavage next week anyway on the NHS without going into the trial they do need to know what those options are. So very often what we do for them sometimes that they have a study explained to them, they don't realise

> that they could have actually had the treatment part of it sooner and definitely without them being randomised, they wouldn't go into the trial at all … that may be quite a factor in making people not be recruited but they have to be honestly told about it.
>
> (MREC 1)

Whether or not participants can withdraw from the study:

> And I would also think would have to be explained to them is again whether a withdraw option at some stage during the follow-up, they decided well actually my knee is getting worse for some other reason a reason which you might have a cartilage problem and if they feel that they are limited to staying in a 2-year follow-up they have agreed to do it and they want to do it so they will not be able to have other surgery during that time if they are going to actually fulfil your sort of intention to treat group and actually going to go through right through to the follow up … patients tend to be terribly loyal once they are in a trial and they sort of put themselves through things that perhaps they shouldn't do if they feel they actually must not have more surgery during whatever that might be the follow-up you will be designing for them.
>
> (MREC 1)

Whether or not participants can access surgery during the follow-up period of the trial:

> When would they receive any first line or surgical treatment for correction of any problems that they may have which if presumably they have osteoarthritis of the knee they would have … And are the people who are having the placebo going to have surgery ultimately?
>
> (MREC 3)

> The usual thing is then that people that have been in the placebo arm should in courtesy should be offered the treatment as soon as possible because they have actually gone through the trials to prove that point and have not received any benefit, and it is usual in the patient information sheet to state whether that is your intention.
>
> (MREC 1)

> Are you going to offer them the real operation if the first one doesn't work?
>
> (MREC 6)

Whether or not participants would ever be told what surgery they had received (and if so, when):

> There's multiple things, for example, what exactly do you tell the patients, when would they find out what they've had.
>
> (MREC 3)

> If arthroscopic lavage is found to be effective, whether or not the placebo group of patients can get access it.
>
> (MREC 1)

Component 4 – Surveys of health professionals

Methods

Postal surveys of orthopaedic surgeons (all members of BASK) and anaesthetists (all members of the BSOA) were conducted. Formal permission to mail the questionnaire to society members was received from both organisations. Approval was received for single mailings only – therefore, follow-up reminders were not possible.

The aim of these short surveys was to investigate the distribution of attitudes towards the proposed trial, and ascertain rates of expressed willingness among these groups to support the trial in their professional capacities. The questionnaires are reproduced in Appendix 9.

In an attempt to maximise our survey response, we also utilised a number of the methods proposed in the review of Edwards *et al.*,[38] which had explored the impact of different interventions on response rates to postal questionnaires. We kept the questionnaire short (one A4 sheet), used coloured ink, gave an assurance of confidentiality, highlighted the importance of the topic to the respondents and also highlighted the university/HTA programme sponsorship of the research.

Results

Survey of orthopaedic surgeons

One hundred and seventy-three (45%) of the 382 surgeon questionnaires issued were returned; five of these were returned blank – giving a denominator of 168 questionnaires (*Table 2*). Eighty-five (51%) supported the idea that a placebo-controlled trial of arthroscopic lavage should be conducted and 71 (43%) indicated that they would be willing to take part in such a trial. Sixty-seven (40%) indicated that, if a friend or a member of their family had osteoarthritis, they

TABLE 2 *Surgeons' perspectives on different types of trials of arthroscopic lavage*

	n **(%)**
Potential trial of arthroscopic lavage vs placebo surgery vs conservative management	
Supportive of trial with placebo arm being mounted (*N* = 168)	85 (50.6)
Would consider taking part in a trial with a placebo arm (*N* = 166)	71 (42.8)
Would encourage a friend or family member to sign up for a trial with a placebo arm (*N* = 168)	67 (39.9)
Potential trial of arthroscopic lavage vs conservative management only (i.e. no placebo)	
Supportive of trial with no placebo arm research being mounted (*N* = 164)	111 (67.7)
Would consider taking part in a trial with no placebo arm (*N* = 161)	93 (57.8)
Would encourage a friend or family member to sign up for a trial with no placebo arm (*N* = 160)	95 (59.4)
Preferred randomisation ratio should a trial with a placebo arm go ahead (N = 147)	
Equal randomisation (1:1:1 to arthroscopic lavage, placebo surgery and conservative management)	88 (59.9)
Unequal randomisation (2:1:1 to arthroscopic lavage, placebo surgery and conservative management)	15 (10.2)
No preference	37 (25.2)
Other randomisation ratio	7 (4.8)

would encourage them to participate in such a trial. Surgeons were asked their opinion on different randomisation ratios (i.e. 1:1:1 or 2:1:1 for arthroscopic lavage, placebo surgery and non-surgical management) should a placebo trial go ahead. The majority of surgeons (60%) felt equal randomisation would be appropriate, with a further 25% expressing no preference.

Results from the survey indicated that 62 (37%) of the surgeons did not routinely undertake lavage. Of these, 23 used to undertake lavage but now did not. The main reasons cited for stopping arthroscopic lavage were unpredictability of outcome and the Moseley trial report. Ninety-nine surgeons provided open comment on the questionnaire. These comments were consistent with the range of views expressed in the focus groups with health professionals, including both negative views:

> Proposed trial is immoral if not unethical to give a general anaesthetic with no procedure.
>
> I would not ask nor expect my anaesthetist to compromise himself.
>
> I cannot support the idea of giving an anaesthetic for a placebo arm of a trial.

and positive views:

> About time.
>
> Although I do not believe in arthroscopic lavage for knee OA [osteoarthritis], I will be more than happy to participate and also encourage other knee surgeons in the department to do so to help sorting this issue once and for all.
>
> Concerns that lavage may be a waste of NHS resources. If a randomised/placebo trial showed this it may change NHS practice …
>
> This trial needs to be done!

Others provided comments on their preferred role for arthroscopic lavage – mainly only in the presence of mechanical symptoms – and provided suggestions on how the trial designed might be refined, e.g. allow hyaluronic acid injection in the conservative arm, restrict to early osteoarthritis, etc.

Survey of anaesthetists

One hundred and thirty-six (34%) of the 398 anaesthetist questionnaires were returned (*Table 3*). Fifty-four (40%) anaesthetists directly supported the idea that a placebo-controlled trial of arthroscopic lavage should be conducted, although a greater percentage (47%) indicated that that they would agree to coparticipate if their orthopaedic surgeon colleague wished to take part in such a trial. Forty-eight (36%) indicated that, if a friend or a member of their family had osteoarthritis, they would encourage them to participate in such a

TABLE 3 *Anaesthetists' perspectives on different types of trials of arthroscopic lavage*

	n **(%)**
Potential trial of arthroscopic lavage vs placebo surgery vs conservative management	
Supportive of trial with placebo arm being mounted (*N* = 135)	54 (40.0)
Would agree to coparticipate in a trial with a placebo arm if orthopaedic colleague wished to take part (*N* = 134)	63 (47.0)
Would encourage a friend or family member to sign up for a trial with a placebo arm (*N* = 135)	48 (35.6)
Potential trial of arthroscopic lavage vs conservative management only (i.e. no placebo)	
Supportive of trial with no placebo arm research being mounted (*N* = 135)	119 (88.1)
Would agree to coparticipate in a trial with no placebo arm if orthopaedic colleague wished to take part (N = 134)	120 (89.6)
Would encourage a friend or family member to sign up for a trial with no placebo arm (*N* = 132)	107 (81.1)
Preferred randomisation ratio should a trial with a placebo arm go ahead (N = 121)	
Equal randomisation (1:1:1 to arthroscopic lavage, placebo surgery and conservative management)	56 (46.3)
Unequal randomisation (2:1:1 to arthroscopic lavage, placebo surgery and conservative management)	12 (9.9)
No preference	49 (40.5)
Other randomisation ratio	4 (3.3)

trial. As with the surgeons, anaesthetists were also asked their opinion on different randomisation ratios (i.e. 1:1:1 or 2:1:1 for arthroscopic lavage, placebo surgery and non-surgical management) should a placebo trial go ahead. The majority of anaesthetists expressed a wish for equal randomisation or expressed no preference. Most anaesthetists (88%) indicated they would also be supportive of a trial where no placebo would be involved.

Many of the anaesthetists (82) provided comments on the questionnaires. For those who were not supportive of a trial that included a placebo procedure, many commented that they would find it unethical to give a general anaesthetic for a placebo procedure. Comments such as:

> Sounds unethical to put a patient under risk by anaesthetising them (even if the risk is 1:100,000,000) for placebo surgery!
>
> I feel strongly that placebo surgery is unethical – anaesthesia has risks!
>
> I do not understand how placebo surgery can be ethical. If persuaded of this I would be happy to participate.
>
> Unethical!

typified their sentiments.

Other comments indicated the complexity of the issues. For example:

> 'Unnecessary' anaesthetics for placebo surgery are justified: if the trial shows lavage to be ineffective then subsequently anaesthetics for ineffective surgery would be avoided.
>
> If the placebo effect is significant, but found to be statistically similar to washout, are we going to give general anaesthesia for knee stabbing alone as a beneficial therapy?…
>
> Whilst the outcome of arthroscopic lavage is uncertain, it remains a recognised procedure. However, placebo surgery exposes the patient to all the risks and side effects of a general anaesthetic knowing that no procedure is being undertaken. I could not justify giving a GA [general anaesthetic] under these circumstances. Should the patient suffer serious consequences I do not believe it can be justified.
>
> A difficult dilemma re the small risks of GA [general anaesthetic].
>
> …the idea of placebo surgery is tricky to implement because anaesthesia of one sort or another is inevitable.

Those supportive of a potential placebo-controlled trial made suggestions to refine the study design

(for example, confining the population to those in ASA grades 1 and 2, standardising on the use of local anaesthetic within the knee space at the end of surgery). The importance of the patient-informed consent was also stressed.

Comments on the acceptability phase

The findings from the acceptability phase of our study have shed light on the views of key stakeholder groups (including surgeons, anaesthetists, prospective participants and members of research ethics committees). The following is an overview of the key findings from both within and across the stakeholder groups.

Views about the rationale for more research into the effectiveness of arthroscopic lavage

There was a broad general acceptance across all stakeholder groups of the need to find out more about the effectiveness or otherwise of arthroscopic lavage, given information about the trial conducted by Moseley *et al.*[24] Whilst prospective trial participants who had osteoarthritis of the knee tended to make favourable comments about the role of research in determining 'best' treatments in general terms (a finding supported by other studies that have explored lay understandings of clinical trials[39,40]), health professionals and chairpersons of MRECs made more specific comments relating to the current general uncertainty with regard to the effectiveness of arthroscopic lavage and the number/cost of procedures performed.

Within the health professional groups, although there was a broad general acceptance of the need to find out more, some individuals were more and some less inclined to be optimistic about the effectiveness of arthroscopic lavage in the face of uncertainty from research evidence. This variation in opinion reflected different ideas and experiences relating to the usefulness of arthroscopic lavage in clinical practice. Those who were more optimistic about the effectiveness of arthroscopic lavage were more likely to question whether both proposed trial arms (arthroscopic lavage and placebo) could be regarded as equal in terms of potential harm or benefit to participants (they were concerned that the placebo intervention would be worse), whereas those who were more sceptical about arthroscopic lavage were more likely to consider that the two arms were comparable. Other studies investigating views about clinical trials have found that health professionals may hold views about trial treatments that are based on different interpretations of the available scientific evidence.[41]

Ethical acceptability of proposed trial

Despite this general acceptance of the need to find out more, there was variation in opinion within all the groups about how researchers should approach this and whether or not it would be acceptable to investigate the effectiveness of arthroscopic lavage using placebo surgery.

Within the health professional groups, there tended to be a split between (1) those who were strongly opposed to the inclusion of a placebo surgery arm on the grounds that it could lead to potential harm among individuals who could expect no personal benefit and (2) those who were more in favour on the grounds that they believed the small risks that relatively few people in a placebo surgery trial arm would be exposed to were justified because they were outweighed by the potential benefit (i.e. potential benefit to future patients and broader society of helping to ensure either that a demonstrably effective surgical procedure was used or that a demonstrably ineffective procedure was not). Although a few clinicians apparently thought their professional ethical codes/personal views would rule out any placebo surgery, most considered issues specific to the proposed trial (including evidence about the intervention to be tested; about the kinds of outcome that might be anticipated; about current practices; about the strength and utility of knowledge that might be derived from placebo-controlled trial versus other methods in this case; and views about optimising the placebo procedure).

The MREC chairpersons attempted to reflect broadly on how they thought their committees would view the proposed trial. Within this group, there was general acceptance that there were some 'good' ethical and methodological arguments for incorporating a placebo component into the proposed design, and that the health professionals we had consulted had made good suggestions about how best to minimise any potential risks of harm from the placebo. However, no surgical placebo procedure can be completely risk free, and MREC chairpersons noted that because MREC

members tended to focus primarily on the interests of prospective trial participants rather than broader society, exposing individuals to potential harm for no personal benefit would be deemed particularly problematic.

For prospective trial participants who had osteoarthritis of the knee, the question of whether or not it would be acceptable to conduct the proposed trial was discussed from a more personalised perspective in the sense that they specifically reflected on their own potential participation and their reasons for or against participating. Most of this group said they would consider taking part and, as well as expressing a desire to help others through their participation, there was a general tendency to down-play any potential risk of harm from their participation whilst emphasising the potential to gain some form of personal benefit (through either the interventions being given within the trial or trial processes). This observation that willingness to take part is amplified by a perception of benefit to self has also been noted by other authors.[42,43] A minority stated that whilst they were supportive of research in general and expressed a desire to help others through research participation, they would be unwilling to take part because of reasons relating to perceptions of uncertainty regarding the potential to benefit (as well as the potential to be harmed) from the interventions being given within the trial. Several previous studies that have explored people's willingness to participate in a randomised trial have reported that people often express unwillingness to take part despite expressing positive attitudes towards research in general.[39,40,44]

The importance of people expecting to benefit personally from a trial has been highlighted in previous studies as having an influence on levels of participation.[45] In agreement with some of our findings, these studies have suggested that some trial participants make assumptions about trial interventions being effective and do not appear to fully appreciate key aspects of clinical trials.

The nature of information that should be provided to prospective participants

Given the nature of our proposed trial, the health professionals and MREC chairpersons we spoke with recognised that particular attention should be paid to the informed consent process when attempting to recruit participants.

The MREC chairpersons in particular discussed in some detail the nature of information that, in their opinion, should be provided to prospective participants. Here, attention was focused on disclosure of the potential harms that may result from participation as well as discussion of the 'rights' of prospective participants. Contributing to furthering medical knowledge and helping future patients was an important consideration for the people with osteoarthritis whom we spoke to (both for those who stated that they would consider participating in the proposed trial and those who expressed reluctance). Several other studies have reported that the potential to help others may be an important motivator for research participation.[46] However, none of the MREC chairpersons highlighted the importance of discussion within trial information of the potential benefits of an individual's participation for others (and perhaps their future selves). This is perhaps unsurprising given MREC members' tendency to focus on protecting the rights of individual trial participants. Indeed, other commentators have noted the tendency for legislation and guidance around research recruitment information to emphasise discussion of potential harms and benefits to individual participants and pay less attention to the importance and acceptability of messages that highlight the potential to help others through research participation.[47] Given that clinical trials are not designed to benefit participants directly and often expose them to risks that are not outweighed by known medical benefits, perhaps there is some scope to incorporate reference to the potential to help others within trial recruitment information.

When discussing the nature of information that should be provided to prospective participants, there was recognition among the MREC chairpersons that ensuring informed consent can be problematic for researchers (for reasons relating to the tendency for trial participants to fail to understand or remember information about uncertainty and randomisation). Indeed, within our interviews with prospective trial participants, despite all of them indicating that they had understood the written information about the proposed trial, some made comments that suggested they had not fully appreciated all the key points. In particular, some participants made assumptions about arthroscopic lavage being an effective treatment. Previous studies that have explored participants' understanding of trial information have reported a higher level of subjective (or perceived) understanding than objective (or measured) understanding.[48,49]

Strengths of the acceptability phase of our study

Although we accessed the in-depth views of a relatively small number of stakeholders within the qualitative component of the acceptability phase of our study, we nevertheless gained valuable access to the multiple perspectives of a range of key people. The survey provided information about the views of larger numbers of surgeons and anaesthetists. As borne out by MREC chairpersons' comments, by involving all key stakeholders early in the planning of such a trial we were able to explore important issues relating to: attitudes to the use of a placebo procedure in the proposed evaluation; the range of placebo procedures that could be considered for a trial comparing arthroscopic lavage with a placebo procedure; whether attitudes to the proposed trial differ depending on the type of placebo proposed and/or key trial design features; and initial suggestions for ensuring recruitment and other procedures are appropriate from a participant perspective.

Potential limitations of the acceptability phase of our study

Facts and arguments incorporated into our initial slide presentations (which were delivered at the start of focus groups) and our information leaflets about the acceptability phase (which were sent out to interviewees) were drawn on by several participants in subsequent discussions, and may have influenced the nature of stakeholders' views. In addition, the KORAL clinicians who assisted in the facilitation of the health professional focus groups played an active part in discussions and may have influenced what other participants felt able and/or willing to say. However, we were careful to provide a balanced overview and to stress that we wanted to investigate whether, and why, a placebo-controlled trial would (or would not) be acceptable. Practical considerations led us to hold focus group discussions in centres where KORAL clinicians worked and at conferences where members of the relevant professional groups were already convened. We had little control over, and did not monitor, the extent to which participants represented clinicians with particular demographic, professional or work situation characteristics. However, this seems unlikely to have impaired our ability to identify the key issues relating to the proposed trial for health professionals. Within the focus groups and interviews a range of different views were expressed and there was often disagreement within the groups, particularly around the key ethical issues of our proposed trial.

Despite setting out to purposively select our sample for the patient interviews and focus groups, there was, inevitably, an element of convenience (or 'opportunistic') sampling in our study in that ultimately we had no control over who agreed to be interviewed from our initial sampling 'framework'. It is possible that this may have influenced our findings; for example, responders' views may have differed from those of non-responders. For example, our sample was generally positive with regard to the rationale for the proposed trial (with most stating that they would consider taking part) and the views of non-responders may have differed. However, we were reassured that despite the general acceptance of the need to find out more, there was variation in opinion within our patient group about how researchers should approach this and about whether or not it would be acceptable to investigate the effectiveness of arthroscopic lavage using placebo surgery (and a minority stated that they would be unwilling to take part for a variety of reasons).

We also observed relatively low response rates to our surveys (45% to the surgeon survey and 34% to the anaesthetist survey). It is possible that those who were particularly interested in the topic responded; however, we were reassured by the fact that a range of opinions was expressed (both positively and negatively) in the questionnaire responses. It is often the case that response rates to surveys of health professionals are low;[50] in our case, this was not helped by the fact that only single mailings were authorised by the professional bodies, so we could not send out reminders about the questionnaire.

We also asked people to discuss a hypothetical trial. It is possible to speculate that views might have differed if stakeholders had been invited to enter and/or comment on a real trial involving placebo surgery. However, for reasons outlined above, the value of accessing opinions about key elements of the trial before actually proceeding is that researchers can attempt to ensure that the real trial is as acceptable as possible to prospective participants.

Chapter 3
The ethics process

Two elements are presented in this chapter. In the first we seek to explore and describe the underlying ethical dilemmas that relate to, and were often experienced in, the KORAL project, and in the second we describe the formal ethics review process for the study.

Ethical debate around placebo-controlled trials

The ethical aspects of placebo controls have been under intense global scrutiny in recent years. Following lengthy deliberation, both the World Medical Association and the Council of International Organisations of Medical Sciences have revised their guidance regarding placebo use in the past decade. Most of the debate has been around the question of whether it is ever acceptable to assign research participants to receive a placebo when a proven active treatment exists. In the context of the KORAL study, the evidence presented in the early chapters of this document showed that considerable debate remains as to the effectiveness of arthroscopic lavage for osteoarthritis of the knee and, therefore, that it cannot be described as proven active treatment. However, whilst it could be argued that this ethical question does not apply to the KORAL study, we recognised that it would be naive not to take account of the recent intense scrutiny of the ethics of placebo controls.

There has also been considerable debate in the literature as to the ethical acceptability of using placebo procedures in surgery. The use of a placebo in an non-pharmacological context is not new – as early as 1959, a placebo procedure was used in a trial of internal mammary artery ligation for angina pectoris where, in a trial of 17 participants, eight participants had their arteries tied (the Fieschi technique) and the other nine underwent only surgical incisions.[51] There was also a series of placebo-controlled trials of electro-convulsive therapy (ECT) in the late 1970s and early 1980s which compared active ECT with simulated treatment.[52–56] Patients in the simulated ECT groups received identical anaesthetic regimens to those receiving 'active' ECT.

The most recent debate on the ethics of placebo surgery was largely triggered by the Moseley trial,[24] as described earlier, and trials of cellular-based therapies for Parkinson's disease.[57,58] In the Parkinson's trials those patients allocated to the placebo intervention had burr holes drilled in the frontal bone of the skull, but not penetrating the inner cortex of the skull. The principal areas of debate have been around whether placebo surgery fulfils two main ethical requirements for research: (1) that risks to participants are minimised; and (2) that risks to participants are reasonable in relation to anticipated benefits.[59]

Several commentators have argued that placebo procedures are ethical for certain trials of surgery[60] and have identified the Moseley trial as an exemplar of good practice in this field.[61–64] The main components of their arguments are that:

- Clinical trials are not designed to promote the medical best interests of enrolled patients, and often expose them to risks that are not outweighed by known medical benefits – accordingly the use of placebo surgery must be evaluated in terms of the ethical principles appropriate to clinical research.
- Surgical procedures of unproven benefit that are currently in routine use also pose a risk to patients.
- Placebo controls are especially appropriate for the evaluation of surgical innovation that has not previously been associated with robust scientific validation and where subjective symptoms of the patient are relied upon as outcome measures.

Others have argued strongly, however, that the use of placebo procedures cannot be justified in the surgical setting, as any surgical procedure carries risks of harm that are greater than those associated with no surgical interventions, – i.e. it fails to fulfil the criterion that risks to participants are minimised.[65,66]

The most comprehensive consensus statement relating to the use of placebo surgery in research contexts was issued by the American Medical

Association (AMA).[67] They suggested that four criteria should be met. In summary, these are that:

1. Surgical 'placebo' controls should be used only when no other trial design will yield the requisite data.
2. Particular attention must be paid to the informed consent process when enrolling participants in trials that use surgical 'placebo' controls.
3. The use of surgical 'placebo' controls may be justified when an existing, accepted surgical procedure is being tested for efficacy. It is not justified when testing the effectiveness of an innovative surgical technique that represents only a minor modification of an existing, accepted surgical procedure.
4. When a new surgical procedure is developed with the prospect of treating a condition for which no known surgical therapy exists, using surgical 'placebo' controls may be justified, but must be evaluated in light of whether the current standard of care includes a non-surgical treatment and the benefits, risks and side effects of that treatment.

Ethical issues specific to the KORAL study

The term 'placebo' is the common label used to describe any substance or procedure a patient accepts as medicine or therapy, but which has no known therapeutic activity. These 'placebos' can, therefore, describe a wide spectrum of substances and therapies from completely inert substances (such as a dummy pill) or more 'active' placebo procedures (such as the placebo procedure described in the KORAL study) when there are no inert procedures available to mimic the active intervention. These more 'active' placebos are designed to mimic the range of non-specific effects (both beneficial and detrimental) experienced by the patient whilst undergoing the active intervention.

For the KORAL study, therefore, this raised the question of whether the use of an 'active' placebo – placebo surgery in this instance – was ethical in this specific situation. On initial consideration, this approach would seem to violate the principle of non-maleficence (i.e. do no harm). On deeper examination of the issues, however, the situation is more complex. In this instance, not conducting the proposed trial also risks one of two further types of harm: dispensing with what is in fact an effective treatment or continuing to offer what is in fact an ineffective surgical procedure (and thus violating the principle of beneficence).

In medical practice, there is often a trade-off between short-term harms with the prospect of a longer term gain – for example, even a simple venepuncture is not without risk – but the risk is accepted if the importance of the test result outweighs the potential harm done. However, this short-term risk is accepted by the actual individual for his or her own longer term benefit, and much of the ethical complexity around the entire field of research ethics centres around the fact that this one-to-one relationship between persons accepting risk of harm and persons hoping for benefit is not necessarily direct. Rather, the weighing up of benefits and risks is done across a group of people. In the KORAL study, we were required to weigh up whether someone who is potentially not the direct beneficiary could reasonably be asked to take the risk related to placebo surgery. The project team believed that, in this case, it was reasonable. This judgement was based primarily on two main arguments:

1. *The nature of the condition*: Osteoarthritis is a chronic and generally progressive, or at least recurring, condition. Whilst there is no guarantee that an individual would directly benefit from the answers this study aimed to achieve, there was a reasonable likelihood he or she would benefit over the longer term. He or she would in future have the opportunity to receive the active treatment (if it were shown to be effective) or to not have an ineffective form of surgical intervention offered. As patients often live with the consequences of osteoarthritis for many years it can reasonably be anticipated that a sizeable proportion of the trial participants could potentially benefit from the results of this trial.
2. *The results of the KORAL acceptability phase*: The empirical findings from the acceptability phase of our study (see Chapter 2) indicated that such a study design was indeed acceptable to many of the patient group who would qualify for inclusion in the trial. These results, which appeared to suggest that patients were more likely to give a favourable view of the proposed design than surgeons or anaesthetists, were a powerful argument in favour of the study. In such a situation, it could even be argued that not to proceed to trial would be unacceptably paternalistic given these results. This needs to be tempered, however, with some thoughts as

to why the patients appeared to find the study more acceptable than the relevant clinicians. The clinicians, whilst appreciating that the risks of an individual procedure may be low were much more likely than any individual patient to have encountered the more extreme consequences of what can go wrong, even with what appears to be a low-risk procedure (for example, life-threatening adverse events or severe wound infections unexpectedly arising in such circumstances). Therefore, the recourse to the immediate conclusion that this represents paternalism is not straightforward and should be tempered by the reasonable impact of professional experience and expertise. However, the fact that, in the KORAL study, there was a reasonable degree of acceptance among surgeons and anaesthetists that the trial did not ask for an unethical level of risk in proportion to the potential benefits of the trial was important.

These arguments, therefore, formed the basis on which the study team believed it was ethical to consider undertaking this research, and formed the basis for their formal application for ethics approval for a formal pilot study of the trial.

Whilst it was not used as an ethical argument, the fact that all groups in the Moseley trial (including the placebo group) reported significant symptom improvement after the procedure also provided some empirical evidence that, in this specific setting, patients might experience benefit from participation in the trial (although the mechanism of that benefit was not fully understood).

The principles of independent ethical review

Before we formally describe the ethics process for the KORAL study, it is useful to revisit the underlying importance of such an independent ethical review, as it provides important contextual information against which the experience of the KORAL study is interpreted (however, those with expert knowledge of this field may choose to move directly to the description of the KORAL experience below). Even with the best ethical intentions, any clinician or scientist, by virtue of individual experience may develop a skewed sense of the balance of risks and benefits involved in a field of research to which he or she is particularly devoted. An orthopaedic surgeon, accustomed to seeing the most severe effects that osteoarthritis can have on individuals, could understandably develop a skewed attitude to the risks and benefits based on his or her experience. Similarly, anaesthetists, accustomed to continually attempting to minimise risk for their patients, may understandably develop an attitude to the risks and benefits that might be skewed in the other direction. Subjecting the research proposal to independent scrutiny by a group of individuals with a much broader outlook safeguards against the risk that individuals may be asked to take risks in research that are out of proportion with the potential benefits even where the motivation of the researchers is beyond ethical question.

The need for appropriate informed consent on the part of the participants is ethically beyond question.[68] Having to present the detailed methods by which appropriate informed consent is proposed to be achieved is another safeguard for both patients and researchers alike.

Finally, an independent committee, in taking into account possible competing interests, can both protect patients from research that may be motivated by factors of which they should (at the very least) be made aware and protect the researchers from subsequent accusations of less than ethical or questionable professional motives for the study.

Application for ethics approval for the conduct of the pilot study

It was against this background of controversy relating to placebo-controlled trials that the KORAL team sought ethics approval to conduct a formal pilot study to assess the full feasibility of mounting a multicentre placebo-controlled trial to evaluate the effectiveness of arthroscopic lavage for osteoarthritis of the knee. As it sought to reflect the design of a full trial, the pilot was to include full consent and randomisation to a placebo surgical arm.

The pilot (full details of the design are presented in Chapter 4) was designed as a two-centre, three-arm trial with randomisation to one of:

- arthroscopic lavage (with or without debridement as the surgeon saw fit);
- placebo surgery; or

- non-operative (medical) management with specialist reassessment.

The components of the proposed placebo surgery were informed by the extensive discussions with the surgeons and anaesthetists (see Chapter 2). As with the arthroscopic lavage, the placebo surgery was to be performed as a day case and undertaken in an operating theatre under general anaesthesia.

Eligible patients were to be recruited from hospital clinics, and if they consented to participate, randomised to one of the three interventions. Participants were to be followed up at 2, 6, 12 and 24 months.

Multicentre Research Ethics Committee approval

An application was submitted for national MREC approval to conduct the pilot study in June 2006 (the application was submitted, as had been agreed, to the MREC that had approved the original acceptability study).

The Multicentre Research Ethics Committee members discussed the application at an initial meeting in June 2006 at which they gave the pilot a 'provisional favourable response' subject to receiving the full report of the initial feasibility phase (preliminary findings had been included, but final data were not available at the time of application submission) and some minor changes to the information sheet. The KORAL team provided this extra information and agreed to attend the following meeting of the MREC to address any outstanding queries.

At the next MREC meeting in August 2006 (which the KORAL Chief Investigator, MKC, attended) the MREC informed the team that a 'provisional favourable response' was assigned only to allow the application to be retained in the system and that the Committee had a number of major concerns about the project. There was extensive discussion about the place of general anaesthesia in such a study, concerns about centres that had stopped carrying out arthroscopic lavage on a routine basis taking part in the pilot and concerns about indemnity for non-negligent harm. They were also concerned about the extent to which this study would add to the original Moseley trial.

Following that meeting, the Committee's written conclusion was that they were unable to give a favourable ethical opinion to the study. An extract from their letter, outlining the reason for this, is presented in *Figure 1*.

The KORAL team reviewed this ethical judgement closely and, following extensive discussions with the lead ethicist (RVC) and consultation with a wider group of ethicists, decided to appeal this decision. It was still felt, based on all of the arguments presented above, that the potential benefits to patients with osteoarthritis of the knee justified the risks associated with the study.

We were particularly concerned that approval for the trial hinged on the issue of whether patients would, or would not, have been routinely offered surgery had the trial not been in place. Two particular issues seemed to be important in the ethics committee's ruling: (1) the inclusion of surgeons who would not normally offer arthroscopic lavage and (2) the inclusion of centres where arthroscopic lavage was being phased out and was no longer a routine treatment choice. In our opinion, surgeons who would never consider offering arthroscopic lavage would be highly unlikely to take part in the trial. Therefore, we could assume that, for patients recruited from surgeons who would take part in the trial, there was at least a theoretical possibility that they might have been offered lavage had the trial not been in place. For those centres that had stopped undertaking routine arthroscopic lavage, but that wished to take part in KORAL to find out whether lavage was truly effective/ineffective (i.e. to find out whether they were making the correct decision to phase out lavage), we believed that this was a further justification for proposing the research, rather than an ethical objection to it. In addition, the empirical evidence from the HES indicated that arthroscopic lavage was still being undertaken in significant numbers across a wide range of centres.

Essentially, it seemed to us that participation in the trial should be deemed either ethical or not, be based on sound ethical principles and not be based on where the patient lived. Consider a hypothetical patient who is eligible for inclusion into the trial living near a centre where lavage was falling out of favour and was no longer routinely performed, but where the clinicians had decided to take part in KORAL as mentioned above. Under the MREC ruling it would be unethical for this patient to be entered into the trial (even if fully informed and wishing to participate). However, if that patient moved to the catchment area of a hospital where lavage was still routinely undertaken this would

Ethical opinion

The Committee is unable to give a favourable ethical opinion of the research as presently designed, for the following reasons:

"The Committee could accept the need for a trial and understand the choice of comparator. It recognised that a feasibility study was necessary properly to assess the acceptability to patients of this approach. It accepted that this could be ethical, provided that patients had been fully informed about risks and chose the trial after proper discussion and time for reflection. However, as there would remain a small risk from the anaesthetic and procedure the Committee considered it unethical to recruit potential participants who would not routinely have been offered surgery and/or whose treating clinician would not routinely carry out an arthroscopic lavage procedure, thus exposing them to the potential risks of surgery purely for research purposes."

FIGURE 1 *Extract from MREC decision letter.*

indicate that, purely by moving house, entry to the trial would become ethical for that patient. This seemed inappropriate and appeared to have parallels with so-called 'postcode' lotteries for treatment whilst still leaving the question of the effectiveness of lavage unanswered.

As such, we appealed the MREC decision – an appeal was allowed and assigned to be heard by a different MREC. The KORAL Chief Investigator (MKC) and Lead Anaesthetist (BHC) attended the appeal meeting on behalf of the KORAL team. This meeting took place in November 2006, where the study documentation was reviewed in detail again and further clarification was provided by the KORAL team where necessary.

In the appeal we stressed again that in the absence of the proposed trial the evidence base available to surgeons would remain dominated by the original Moseley trial[24] – a trial in which all the procedures were carried out by a single surgeon, in a single US centre, in an atypical group of patients. As indicated earlier, generalisation of the results from the Moseley trial to the practice of multiple surgeons in multiple centres in a different health-care setting has significant limitations.

In addition, we re-emphasised the 12 months of feasibility work that had contributed to the work-up of the pilot protocol, reiterating the findings and especially the acceptability of the trial to potential participants, and to a range of anaesthetists and surgeons, given appropriate informed consent.

Following this meeting, the appeal MREC ruled that they were content to give a favourable ethical opinion of the research subject to 'receiving a significantly revised and extended patient information leaflet'. The appeal committee deemed that the 'quality of the informed consent was crucial in this study' and as such wished the patient information leaflet to be extensive, with particular emphasis to be placed on outlining any potential disadvantages of taking part.

This extensive revision of the patient information leaflet was undertaken by the KORAL team, following which full ethics approval for the pilot study was received in March 2007. A copy of the final version of the MREC-approved patient information leaflet is presented in Appendix 10.

Indemnity

Following the concerns raised in the feasibility phase and in the open discussion at the initial MREC meeting about the issues of indemnity and non-negligent harm, the KORAL team sought to clarify the situation for NHS patients. We sought clarification from the Department of Health, the HTA programme, the Medical and Dental Defence Union of Scotland and the lead institution's clinical trials' insurers.

Our discussions with these multiple agencies highlighted that the issue of indemnity (and particularly non-negligent harm) was rather opaque and that delineation of liability was somewhat unclear. Whilst the NHS institutions accept liability for negligent harm caused by the design of studies they initiate, NHS indemnity does not provide no fault compensation for non-negligent harm.[69] In the KORAL project, whilst the Department of Health was the study sponsor (note – the Department of Health no longer takes on

sponsor responsibility for projects funded through the HTA programme), it was indicated that the primary responsibility for ensuring indemnity cover lay with the 'contractor' (the person who had been awarded the research contract) and his or her employing organisation, rather than remaining a sponsor activity.

For the KORAL pilot, we ensured that the project had written confirmation from the lead institution's clinical trials' insurers that appropriate insurance arrangements were in place for the study. In addition, the host institution held a 'no fault' insurance policy. This policy covered all employees of the institution and those working under their direction.

Comments on the ethics process

Placebo-controlled trials give rise to complex ethical questions. These are intensified when it is proposed that an 'active' placebo be used to mimic the range of non-specific effects (beneficial and potentially detrimental) that a patient might experience under the active intervention. For some conditions, however, without such trials it will never be possible to know whether or not a specific procedure is more effective than placebo. As such, it may be ethically justified to use surgical placebo in some situations, provided the potential risks have been carefully evaluated and are outweighed by the potential benefits.

The ethical review process is a crucial safeguard for studies such as this. Understandably it can become long and complex. This has the drawback of postponing the answers to the research question proposed. Whilst bureaucratic delays to this process should be minimised, it is essential that the genuine ethical dilemmas be explored and debated fully.

Genuine informed consent is particularly important in the context of 'active' placebos, as patients must be fully aware that they are accepting certain risks of the treatment (in this case general anaesthetic) and will not receive any of the benefits (except for those based on the placebo effect itself).

In our case, the indemnity procedures were unduly complex. It would be helpful if the national arrangements for indemnity and non-negligent harm are clarified for all researchers involved in the conduct of clinical trials – particularly those trials that might involve a placebo arm – and perhaps NHS-wide indemnity procedures could be developed by the respective Health Departments.

Chapter 4
The pilot study

Aim and objectives of the pilot study

The overarching aim of the pilot study was to assess the feasibility of mounting a multicentre placebo-controlled trial to evaluate the effectiveness of arthroscopic lavage for osteoarthritis of the knee. The design of the pilot was informed by the extensive qualitative feasibility work (presented in Chapter 2) and the specific ethical issues discussed in Chapter 3.

The specific objectives of the pilot study were to:

- examine whether the trial processes as planned were appropriate, feasible and acceptable to patients, clinicians and the trial office staff;
- quantify the throughput of eligible patients;
- quantify the number of patients approached and the proportion of patients who would accept randomisation to the trial (reasons for refusal were collated to examine whether they were influenced by the inclusion of a placebo procedure); and
- examine the acceptability of the trial information material to patients.

Design of the pilot

The pilot was designed as a two-centre, three-arm randomised trial comparing:

- arthroscopic lavage (with or without debridement at the clinical discretion of the surgeon)
- placebo surgery
- non-operative (medical) management with specialist reassessment.

Eligible patients were recruited from hospital clinics and, if they consented to participate, randomly allocated to one of the three interventions. Participants were to be followed up at 2, 6, 12 and 24 months. A schematic summarising the design of the pilot study is presented in *Figure 2*.

Descriptions of interventions used in the pilot

Arthroscopic lavage

Arthroscopic lavage (with or without debridement as deemed clinically necessary) was to be performed as a day case (unless there were medical or geographical reasons for an overnight stay) and undertaken in an operating theatre under general anaesthesia. A tourniquet could be used on the upper thigh, with either formal exsanguination of the leg or elevation (in line with the surgeon's standard practice). After sterile preparation and draping, the arthroscope was to be inserted into the knee joint via a lateral parapatellar stab arthrotomy, and a probe inserted via a medial parapatellar stab arthrotomy. A further lateral suprapatellar arthrotomy would allow insertion of a drainage cannula. An ordered inspection of the joint and the intra-articular structures would follow. The joint was to be lavaged with several (at least 3) litres of warm saline and any loose debris washed out. A further debridement to remove larger loose bodies and trim frayed meniscal edges, minor tears or osteophytes could then be carried out at the surgeon's discretion. The irrigation fluid was then to be drained from the knee and the arthroscope removed. According to clinical judgement, the arthroscopy portal incisions could be sutured or closed with suture strips, and then dressed. Local anaesthesia would be inserted into the knee space at the end of surgery for postoperative analgesia.

Placebo surgery

The components of the proposed placebo surgery were informed by the extensive discussions with the surgeons and anaesthetists (see Chapter 2). As with the arthroscopic lavage, the placebo surgery was to be performed as a day case (unless there were medical or geographical reasons for an overnight stay) and undertaken in an operating theatre under general anaesthesia. A tourniquet could be used on the upper thigh, with either formal exsanguination of the leg or elevation (in line with the surgeon's standard practice). After sterile preparation and draping, three small (1 cm) skin incisions, penetrating only the epidermis, were to be made

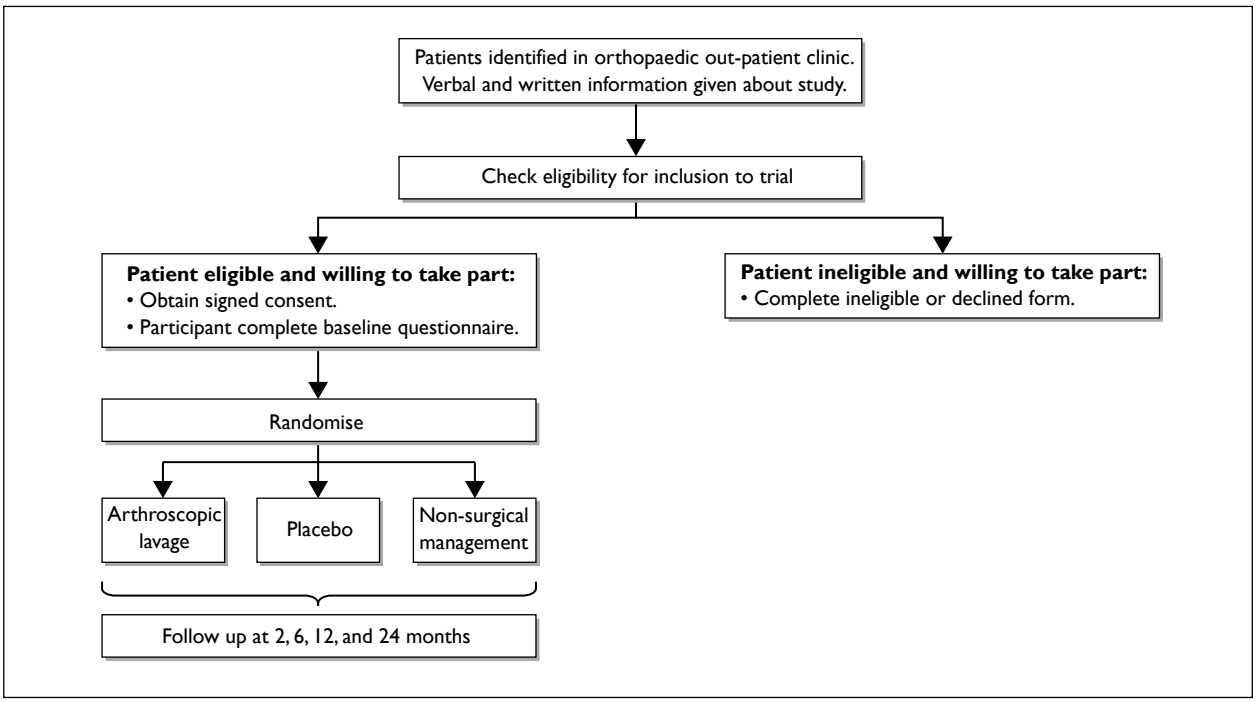

FIGURE 2 *Schematic representation of the design of the pilot study.*

in the same medial and lateral parapatellar and lateral suprapatellar positions as for a standard arthroscopy. There was to be no penetration of the knee space. As with arthroscopic lavage, the incisions could be sutured or closed with suture strips (depending on clinical judgement) and then dressed. Local anaesthesia would be inserted into the incisions for post-operative analgesia. Patients were to be kept in theatre for a similar time to that required for lavage (approximately 20 minutes).

Non-operative (medical) management with specialist reassessment

Management of osteoarthritis of the knee incorporates a range of options, and the management in the 'non-operative' management group was, therefore, based on a specialist reassessment and recommendation of care (other than arthroscopic lavage), taking into account previous management. The expectation was, however, that the management recommendation would include a form of treatment that had not been tried before but which seemed most appropriate to the surgeon responsible for care. The specific 'non-operative' management regimen for an individual patient was left to the discretion of the enrolling surgeon. It could draw from a range of management options, including pharmacological management, physiotherapy and the provision of intra-articular injections. Details of the 'non-operative' management for each patient were to be routinely recorded.

Permissible changes to treatment following randomisation

Once patients had been randomised to a particular intervention arm, no change in treatment was allowed for 3 months (other than in analgesia use). This was to ensure that the short-term effects of each intervention could be examined, without imposing a longer term treatment embargo on patients for whom the allocated procedure had not resulted in relief of symptoms. A 3-month timeframe also fitted well with current UK practice, as many patients are reviewed by the orthopaedic surgeon 3–4 months after arthroscopy.

Eligibility criteria

Patients were eligible for inclusion if they were: (1) adults (18 years or older) with radiological evidence of osteoarthritis of the knee who might be considered for arthroscopic lavage; (2) fit for general anaesthetic – defined by the ASA grade 1 and 2; and (3) able to give informed consent.

Excluded patients were those for whom the orthopaedic surgeon judged that arthroscopic lavage was clearly indicated; for whom arthroplasty was clearly indicated; who had clear contraindication to general anaesthesia; who were unable to speak English; and who had an inability to complete follow-up questionnaires.

Obtaining consent

Potentially eligible patients were provided with the patient information sheet (see Appendix 10) in the outpatient clinic. The dedicated local recruitment co-ordinator discussed the study and went through the patient information sheet with the patients. If required, the patient was given time to decide whether or not to participate. If the patient wished to join the trial, the recruitment co-ordinator checked that the consent form had been understood, and obtained written consent (see Appendix 11).

The participant was also asked to complete a baseline questionnaire whilst at the clinic or, if necessary, at home (see Appendix 12).

If the potential participant did not wish to join the trial, the reason for this decision was explored. It was stressed that this information was sought for the benefit of the trial rather than to try to encourage participation.

Randomisation and allocation to trial group

Once consent was received, patients were randomised to one of the three trial groups using a fully automated computerised telephone randomisation provided by the Centre for Healthcare Randomised Trials (CHaRT), based in the Health Services Research Unit, Aberdeen, UK. CHaRT was the accredited clinical trials unit supporting the KORAL study. Allocation incorporated minimisation on centre and key prognostic factors including age group (≤ 50 or > 50 years), gender, extent of osteoarthritis (whether radiological evidence indicated 'bone-on-bone' or 'non bone-on-bone') and whether mechanical symptoms were present or not. For patients who presented with osteoarthritis in both knees (and for whom arthroscopic lavage might be considered for both knees), the knee indicated by the patient to be the most painful was the knee that was designated the study knee for the purposes of randomisation and subsequent study.

Outcome measures

The primary aim of the pilot was to assess the feasibility and acceptability of procedures for a full trial. However, if it transpired that a decision was made to proceed to full trial, it was hoped that any participant recruited to the pilot would be later integrated into the full trial; thus we planned to follow up pilot participants up at the timings proposed in the main trial (at time points equivalent to 2, 6, 12 and 24 months after surgery) using full trial paperwork.

The outcome measures proposed for the full trial were informed by a study investigating the priorities of patients with osteoarthritis of the knee which showed that the outcomes that mattered most to patients were limitations of activities and pain.[70] Further work[71] on osteoarthritis outcome measures indicated that pain falls within the impairment component of the World Health Organization International Classification of Function (i.e. impairment, activities and participation)[72] and that the recognised knee quality of life score – the Oxford Knee Score[73] – contains items giving pure assessment of pain impairment and activity limitation. By including the Oxford Knee Score and the Short Form (12 questions; SF-12),[74] the full trial would record measurements on all three components (impairment, activities and participation), whilst focusing on the patient's perspective through the use of self-completion questionnaires.

Reflecting this approach the following outcome measures were chosen:

- *Primary outcome measures*: condition-specific pain and disability, as measured by the Oxford Knee Score; knee pain, as measured by a 10-cm visual analogue pain score (and the pain dimensions of the Oxford Knee Score and the SF-12 scales).
- *Secondary outcome measures*: general quality of life, as measured by SF-12; patient utility, as measured by the EuroQol-5 dimensions (quality of life instrument; EQ-5D);[75] non-steroidal anti-inflammatory drug or analgesic use; use of other treatments outside the trial interventions; use and cost of health services; cost-effectiveness – as measured by the incremental cost per quality-adjusted life-year gained.

Questionnaires are reproduced in Appendix 12.

Sample size and feasibility

As this was a pilot study with the explicit aim of refining estimates of likely throughput of patients and the proportion of eligible patients who would consent in a given time period (both of which would inform a sample size calculation for a full trial), a formal sample size calculation at this stage was inappropriate.

Analysis plans

A single principal analysis was planned for the end of the pilot phase. Analysis was to consist primarily of descriptive statistics including throughput per month, proportion of eligible patients randomised, and reasons for refusing to take part in the trial. Reflecting the small sample size, no analysis was to be conducted by randomised group.

Pilot experience

Local approvals – Centre 1

Following receipt of MREC approval, the KORAL team moved to complete internal authorisations for the study to proceed in Centre 1. Local ethics and research and development approvals were received relatively easily, although there were some discussions about the treatment costs for placebo surgery should this pilot eventually move to a full trial. Clinical approval for the study was not so straightforward, however, as there were significant concerns raised at directorate level about authorising such a trial (which included a placebo surgical arm, and especially one that involved general anaesthesia for the placebo) to be conducted within the hospital. The Directorate refused to authorise the study without full discussion of the study by the Regional Anaesthesia Senior Staff Committee – this meeting took place in May 2007. The KORAL Chief Investigator (MKC) and Lead Anaesthetist (BHC) attended that meeting on behalf of the KORAL team and presented the findings of the feasibility study to the committee. The meeting generated extensive discussion, with a range of opinions expressed (both strongly positive and strongly negative). A private vote was taken by the membership of the committee as to whether the trial should be allowed to proceed, which resulted in the trial receiving majority approval. Caveats were applied to the conduct of the study however – only consultant anaesthetists would be allowed to take part in the study and surgery must be undertaken in the main hospital theatre suite (some orthopaedic operations were being undertaken in a mobile unit at that time).

Local approvals – Centre 2

Clinical authorisation also proved challenging in Centre 2. As per local procedures, authorisation was initially referred to the Surgical Directorate. Given the potentially controversial nature of the trial, the study was then referred up to the Divisional Directorate for approval. As in Centre 1, authorisation was deferred until there was full discussion by the Anaesthetic Committee Meeting. The KORAL Chief Investigator (MKC) and Lead Anaesthetist (BHC) wrote a briefing paper for the Committee summarising the results of the feasibility study and the plans for the pilot phase. The Anaesthetic Committee met in October 2007, at which the decision was made that the study could proceed in Centre 2.

A further issue was then raised by Centre 2. In the period since KORAL was originally funded, the centre had stopped undertaking arthroscopic lavage as a routine procedure. As such the centre could now become a recruiting centre only if commissioners agreed to pay the normal 'Payment by Results' tariff for cases (including placebo cases). This led to extended negotiations with the commissioners, who finally agreed to provide funding for a maximum of five cases within the pilot (further negotiations would have been required if the pilot had progressed to full trial).

These local approvals were only finalised in November 2007, and whilst this eventually allowed the site-specific ethics form for the centre to be submitted, a response was not received within the planned duration of the pilot. The local ethics committee requested further information about the centre co-ordinators, but this was not followed up as the decision had, by that time, been taken not to progress to full trial (see Chapter 5). As such, we could not proceed to formal recruitment in Centre 2 in the timeframe of the pilot.

Identification of patients

Referral letters to KORAL surgeons in Centre 1 were assessed for potentially eligible patients, and dedicated KORAL study clinics were set up. The centre's lead surgeon led the majority of the clinics with support from the local KORAL recruitment co-ordinator. The first clinic took place in July 2007. During the period of recruitment

(July–November 2007), eight KORAL clinics were held. Of the 49 patients who were given a clinic appointment, 40 attended (*Figure 3*). Twenty-seven patients were found to be ineligible. Nine of those had minimal pain and were discharged, four were referred for magnetic resonance imaging scan, three had mechanical symptoms (and were referred for arthroscopy), three were given review appointments for a later date, two were listed for knee replacements and two required hyaluronic acid injections. Two of the other ineligible patients had other chronic conditions, another had a meniscal tear and the final patient was referred to the pain clinic.

Of the 13 eligible patients, nine were recruited into the pilot study in Centre 1. Six of these were randomised to some form of surgery (placebo or active) and three were randomised to non-surgical management. Reasons given by those four patients who declined were: one felt the research was important but was not for them; one indicated their pain had reduced since referral (but if it had remained at the same level they would have taken part); one had a new job and had 'plenty to cope with already'; and one did not like the idea of the study.

Table 4 shows the baseline characteristics of the pilot participants. Four patients were male and five female. Of the nine patients recruited, eight completed a baseline questionnaire, comprising the Oxford Knee Score, SF-12 and EQ-5D. One participant, who took the questionnaire home to complete, failed to return it.

Baseline scores on the Oxford Knee Score ranged from 13 to 31 [possible scores range from 12 (least difficulties) to 60 (most difficulties)], with a mean score of 26.5 and a median score of 29. The range of EQ-5D scores was 0.66–0.80, with the mean score 0.74 [standard deviation (SD) 0.06] and median score 0.76 [interquartile range (IQR) 0.69 to 0.80]. Possible scores for EQ-5D range from –0.59 to 1.00 (with higher scores indicating better quality of life).

Seven people completed all questions contained within the SF-12 (possible scores range from 0 to 100, with higher scores indicating better quality of life). On the physical component summary scale, the range of scores was 33.9–49.8, the mean score 42.1 (SD 6.1) and the median score 43.1 (IQR 37.1 to 49.3). On the mental component summary scale, the range of scores was 29.2–61.1, mean score 53.3 (SD 11.2) and the median score 57.5 (IQR 49.7 to 60.2).

TABLE 4 *Baseline characteristics of trial participants*

Characteristic	Description
Gender	4 male, 5 female
Age	
Range	43–63 years
Mean	57 years
Median	61 years
Affected knee	6 right, 3 left
Oxford Knee Score	
Range	13–31
Mean score (SD)	26.5 (6.2)
Median score (IQR)	29.0 (24.5 to 30.5)
EQ-5D	
Range	0.66–0.80
Mean score (SD)	0.74 (0.06)
Median score (IQR)	0.76 (0.69 to 0.80)
SF-12 – physical	
Range	33.9–49.8
Mean score (SD)	42.1 (6.1)
Median score (IQR)	43.1 (37.1 to 49.3)
SF-12 – mental	
Range	29.2–61.1
Mean score (SD)	53.3 (11.2)
Median score (IQR)	57.5 (49.7 to 60.2)
Pain – visual analogue scale	
Range	2–6
Mean score (SD)	3.88 (1.36)
Median score (IQR)	3.5 (3.0 to 5.0)

Patients were also asked to rate their pain 'today' on a visual analogue scale from 0 (no pain) to 10 (worst pain imaginable). The scores reported ranged from 2 to 6, with mean score 3.88 (SD 1.36) and median score 3.5 (IQR 3.0 to 5.0).

What happened to the participants after randomisation

The three patients randomised to non-surgical management were reassessed on the same day as the recruiting clinic, following randomisation. All three were advised on analgesic use. Two

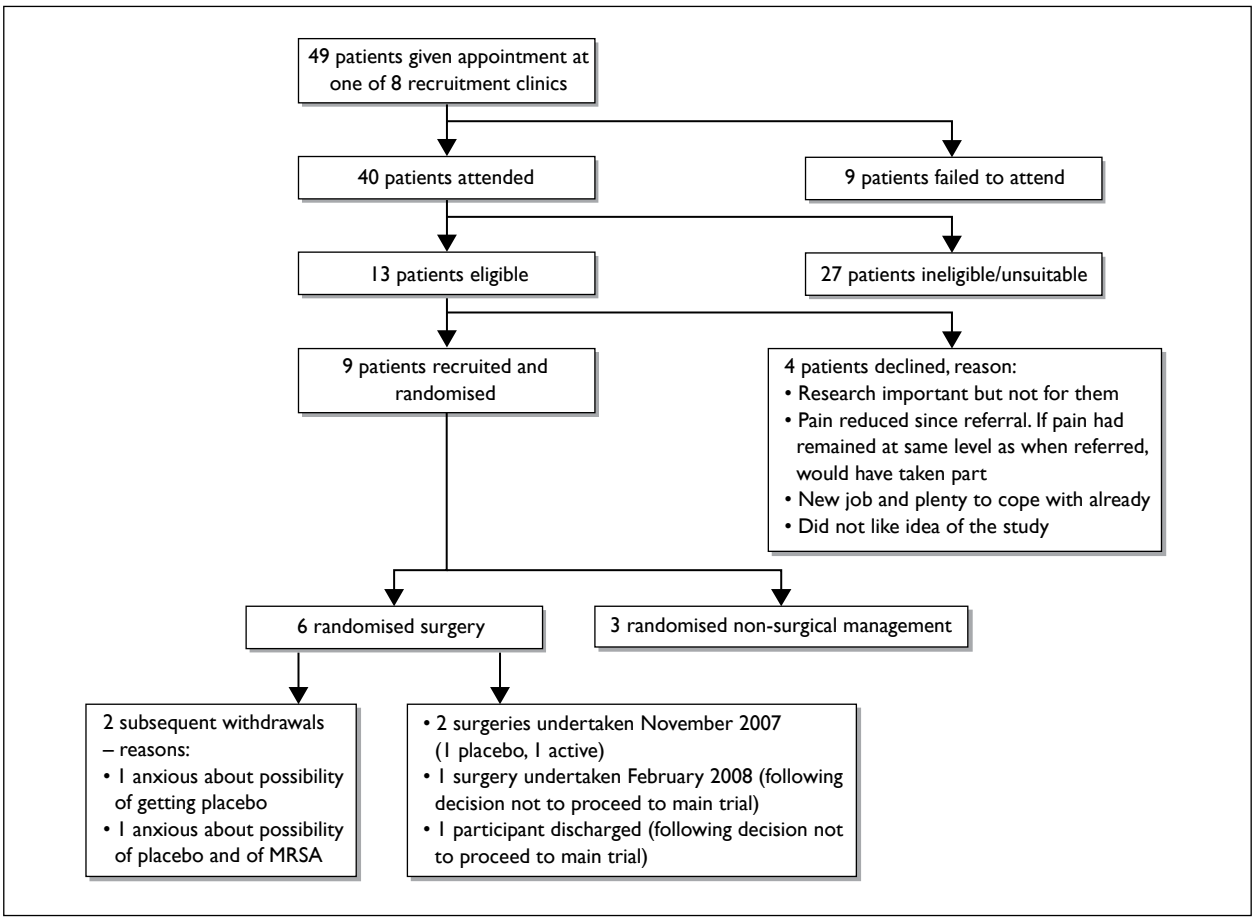

FIGURE 3 *Flow diagram of patients through the pilot. MRSA, methicillin-resistant* Staphylococcus aureus.

participants were given lifestyle modification advice and exercise information. The use of a walking stick was suggested to one participant but this was declined. Two participants were advised to use an elastic knee brace and one was advised on the use of heat and ice.

Two out of the six patients randomised to receive surgery subsequently withdrew from the pilot prior to surgery – both cited anxieties about the possibility of receiving placebo rather than active surgery among their reasons for withdrawal. One participant who withdrew also reported anxieties about the risk of contracting methicillin-resistant *Staphylococcus aureus* (MRSA).

The first KORAL surgical procedures were undertaken in November 2007 when one placebo and one active surgery were performed. The placebo surgery followed closely that laid out in the protocol: the patient was taken into theatre and arthroscopic equipment set up; a tourniquet was applied, the leg exsanguinated and the tourniquet inflated; the three standardised skin incisions were made with a scalpel, taking care not to penetrate the joint capsule; local anaesthetic was injected via a lateral parapatellar approach, dressings and bandages were applied, the tourniquet was deflated and anaesthesia was reversed before the patient was taken to recovery. The patient undergoing active surgery underwent the same process, except that the incisions were completed into the joint, to allow passage of arthroscope, instruments and drainage port; the interior of the joint was examined thoroughly and findings noted. There was no requirement for debridement in this case, and so the joint was lavaged with 3 litres of saline, before completion of the procedure with removal of instruments; dressings were then applied, local anaesthetic injected and bandages applied, before release of the tourniquet and reversal of anaesthesia, as for the placebo patient. Postsurgery, discussion with both patients followed the pre-agreed approach: 'you know that I cannot tell you whether you had the active surgery or the placebo, but I can tell you that the procedure went well

and we will now need to see how well this helps your knee'. This approach was maintained during follow-up clinic appointments.

The two remaining patients who were scheduled for surgery had their management reviewed when the decision was made not to progress to full trial (see Chapter 5), as the decision to stop occurred before their scheduled surgery date.

The three non-surgical participants were all followed up in a hospital clinic approximately 2 months after randomisation. Two of the participants were referred for hyaluronic acid injections and one was placed on the waiting list for knee arthroscopy.

The surgeon reported that the practicalities of the surgical interventions (both active and placebo) presented no significant problems.

The anaesthetist also shared his views with us about administering general anaesthetic to these first two patients. In discussing his views about the ethical acceptability of the trial, in similarity to the position held by several other anaesthetists and surgeons who took part in our focus group discussions, he indicated that although the trial might not result in any personal benefit for individual trial participants, the likely benefits would be that it would provide robust evidence of whether arthroscopic lavage was effective or not for future patients with osteoarthritis of the knee. Although he stated that anaesthetists are trained to avoid risk (and by implication therefore, some anaesthetists would be uncomfortable with anaesthetising a patient for a placebo procedure that would carry a degree of risk), he argued the additional point that, out with clinical trials, many surgical procedures that require general anaesthetic are performed on patients who are unlikely to receive any personal benefit (for example, for reasons relating to the skill level of the operating surgeon, or the appropriateness of the procedure for a particular patient). He also argued that as long as health professionals have attempted, wherever possible, to limit risks to patients, the crucial issue is the extent to which informed consent is obtained from the patient before any operation takes place.

In terms of his experience of taking part in the pilot trial, he discussed how he had been unaware of the patients' group allocation until after they had been anaesthetised and brought into the operating theatre (where the allocation was then revealed to both the surgeon and the anaesthetist). Although the anaesthetist stated that he personally did not feel any differently towards the two patients after their allocation was revealed (and was primarily focused on getting them through the operation and into recovery as safely as possible), he discussed how the theatre staff had expressed some concern when it was revealed that one of the patients was to receive placebo surgery (despite the fact that the theatre staff had been fully aware of the nature of the trial prior to their participation).

Postal follow-up

The randomised participants who remained in the pilot were followed up at the intended time points (the two patients who had surgery and the three who had conservative management). Of the two patients who had surgery (one active, one placebo), in the 2-month follow-up questionnaire, neither patient reported that they thought they had undergone placebo surgery. At this point, both patients reported their pain as '1' on the visual analogue scale (out of 10). Of the three patients randomised to conservative management, two reported their pain as '7' on the visual analogue scale at their 2-month follow-up, the other reported a rating of '2'.

Comments on the pilot study

The pilot study showed that, in principle, a placebo-controlled trial in surgery can be conducted. It showed that a significant proportion of patients were willing to participate in a trial that would involve a placebo surgical arm, and that it was possible to undertake placebo surgery successfully and blind patients to their allocation.

The experience of the pilot, however, showed that, despite full MREC approval, the study required major discussion and negotiation before local clinical approvals could be obtained. Many of the arguments raised at MREC level were raised again at local level, and the fact that ethics approval had been granted did not mean that clinicians would automatically accept that the process was ethical. The ethics of a placebo-controlled trial in surgery remained contentious and there was a number of individuals (mainly anaesthetists) who retained strong negative perceptions of the ethics of the trial. However, we would anticipate that the wide airing the ethical arguments received through the process of securing consent for the pilot

stage would make the process of obtaining ethics approval for a full trial less onerous.

Once clinics were under way, a significant percentage of eligible patients appeared willing to participate in the study – although once patients knew their allocation, some of those allocated to surgery became more concerned about the possibility of undergoing placebo surgery, and some withdrew. This suggested that higher than normal rates of postrandomisation withdrawal might have been expected in those randomised to some form of surgery should the study have progressed to full trial. However, the number of patients involved in the pilot was small, and as such strong conclusions cannot be made as to the true proportion of patients who would agree to participate and the proportion who might drop out of a full trial.

The issue of how, in a full trial, a placebo procedure would be funded in the context of different local commissioning arrangements remained unclear. This would have to be addressed on a case-by-case basis which is logistically cumbersome in a multicentre trial.

Chapter 5

The decision-making process

The decision-making process

Because of the multiphase nature of the study and the need to move rapidly between stages, a bespoke decision-making process for the project was set up with the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC; formerly known as NCCHTA). At the start of the project it was agreed that special decision-making teleconferences would be held for the end of each of the distinct phases of the study to allow decisions to be made in a timely manner. At each teleconference a recommendation would be made as to whether the project should continue on to the next planned phase or the study should close. The grant holder team undertook to deliver specific project reports ahead of these teleconferences in addition to the standard progress reports required every 6 months. These decision teleconferences involved staff from the NETSCC, an independent scientific chairperson and the grant holder team. Final decisions were made by the NETSCC (in consultation with the independent scientific chairperson) and fed back to the grant holder team in writing.

The first decision teleconference was planned for the end of the feasibility phase. The aim of this teleconference was to review the findings of the (mainly qualitative) feasibility phase and to decide if there was sufficient support from those interviewed to allow the project to continue to a formal pilot phase.

The second teleconference was planned for the end of the formal pilot phase. The aim of this teleconference was to review the results of the pilot and to decide if the pilot experience, set against the current clinical climate, was conducive to progressing to a full-scale trial.

The first decision-making teleconference – end of the feasibility phase

The first decision-making teleconference took place in June 2006. At this point, data were available from all the qualitative components of the study and from the surveys of surgeons and anaesthetists. As highlighted in Chapter 2, these data showed that a range of views had been expressed on the acceptability of a placebo-controlled trial. A number of surgeons, anaesthetists and potential participants, however, had shown willingness to participate in such a trial if it went ahead.

Nevertheless, we were aware that all the responses in the feasibility phase were related to a hypothetical scenario. No one was being asked to actually participate in such a trial, and it was possible that, if a placebo-controlled trial were mounted, attitudes might change (or that there might be a mismatch between the attitudes of the surgeon and his or her corresponding anaesthetist in different centres), leading to very different sign-up rates. It was difficult to predict take-up rates without moving to a 'real-life' scenario.

At the teleconference, these issues were fully discussed and the conclusions reached that:

- There appeared to be sufficient numbers of health professionals willing to consider participation in a placebo-controlled trial.
- Potential participants also showed willingness to take part.
- It was crucial that better estimates of realistic 'take-up' rates be explored and that this would be best achieved through progression to the small-scale formal pilot study.

As such, the decision was made at that time to progress, as initially planned, to the formal pilot phase.

The second decision-making teleconference – end of the pilot phase

The second decision-making conference took place in January 2008. At this point data were available on: the experience of gaining ethics approval; the experience of gaining local approvals at the two pilot centres; the flow of patients from all eight KORAL clinics that had been held in Centre 1; all

randomisations (and any subsequent withdrawals); the initial experience of all the non-surgical management patients; the experiences of the first two surgical procedures (one active and one placebo procedure); and information on the trends of arthroscopic lavage use in the UK over recent years.

This pilot study had shown that:

- The perceived ethics of a placebo-controlled trial in surgery remained contentious (even after ethics approval was received). There were a number of individuals (mainly anaesthetists) who retained strong negative perceptions of the ethics of the trial. However, given that the ethical principle of the trial had been given an extensive airing through the pilot study, one would expect that ethics approval for a continuation of pilot to full trial would be less onerous.
- Even when ethics approval had been received, approval at a local level was not straightforward. Many of the arguments considered at the ethics committee stage were raised again at local level. Had the study progressed to full trial, the experience of the pilot suggested that ensuring appropriate authorisations in multiple centres could have been a lengthy and time-consuming process.
- The issue of how, in a full trial, a placebo procedure would get funded in the context of different local commissioning arrangements was unclear.
- Eligible patients were open to the idea of participating in a placebo-controlled trial, and most of those approached were willing to consent.
- It was possible to undertake placebo surgery successfully and to blind patients to their allocation.
- Had the study progressed to full trial, however, higher than normal rates of post-randomisation withdrawal might have been observed in those randomised to some form of surgery – in the pilot two out of the six randomised to surgery withdrew citing increasing concerns about the possibility of receiving placebo surgery.

The decision whether to proceed to full trial was also informed by data on trends in the usage of arthroscopic lavage (and debridement) in the UK. Data were available from the HES[13] for England and Wales, and data available from 1998–9 to 2005–6 are presented in *Figure 4*. These data showed that the use of arthroscopic lavage, and its associated procedures such as debridement, was steadily declining with a slightly more marked decrease after the publication of the Moseley trial in 2002.

Taking the results of the pilot experience and the trend data on the background usage of arthroscopic lavage together, the conclusion was made that whilst the KORAL pilot had shown that, in principle, a placebo-controlled trial in surgery could be conducted (and that conducting a full-

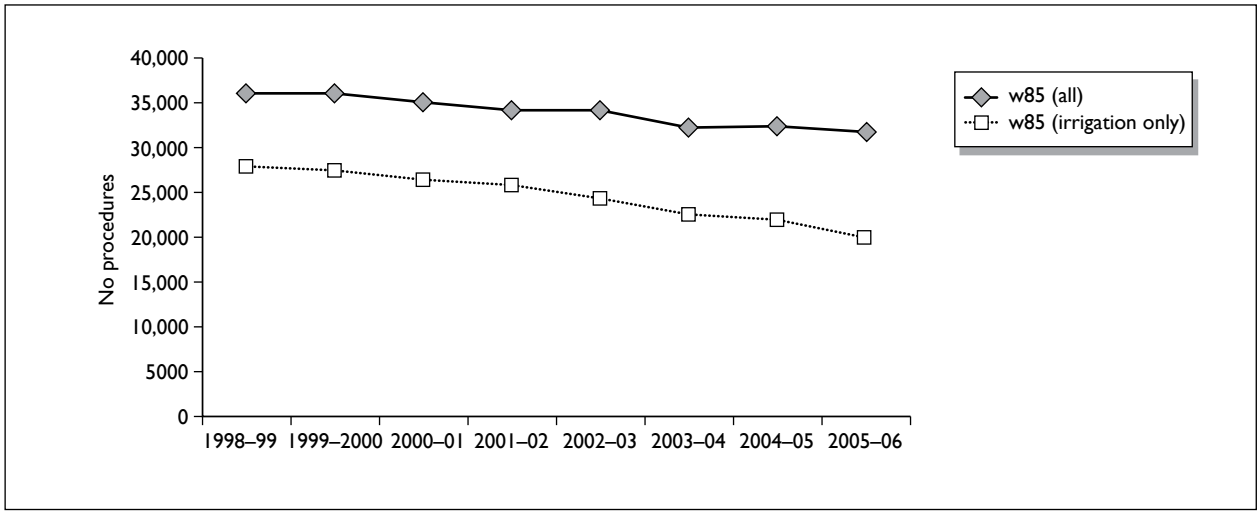

FIGURE 4 *Hospital episode statistics on arthroscopic lavage and associated procedures.*

scale trial in the field was likely to be possible), the anticipated time, energy and cost required to bring multiple centres on board against a background of falling use of the technique was not justified. An extract from the formal decision letter summarising these points is shown in *Figure 5*.

Thus, the decision was made not to proceed to full trial.

Close down

In light of the decision not to proceed to full trial, the KORAL study rapidly moved into a close down phase. Decisions on how to deal with randomised patients still active in the trial had to be made quickly. As the KORAL team knew that close down was always a possibility, close down plans for different scenarios had already been made within the group, which greatly facilitated the transition to close down. These plans were agreed with the MREC.

When the decision was made not to progress beyond the pilot stage, pilot participants fell into three distinct groups. Management of the patients differed according to their grouping:

1. *Those who had already undergone surgery.* Two participants had been randomised to, and had undergone, surgery (one placebo, one active) before the decision not to proceed to full trial. In line with the protocol and the information they were given before their entry into the trial, they were not subsequently informed of the type of surgery that they had undergone. Both patients were invited to attend (as per protocol) follow-up 3 weeks after their surgery; one attended and one did not (despite being offered more than one appointment). If a clinical need arises at some point in the future, plans have been put in place allowing them to be told, if necessary, what procedure they underwent.
2. *Those who had been randomised to surgery, but had not yet undergone surgery.* Two participants had been randomised to surgery (one to placebo surgery, one to active surgery), but at the time of the decision teleconference they had not yet received their surgery. In light of the decision not to proceed, it was agreed that these participants would not progress within the KORAL framework. This was agreed with the MREC. In Centre 1, these patients would not routinely have undergone arthroscopic lavage outside of the trial. It was agreed that these participants would be seen again by the surgeon at the outpatient clinic. At this appointment he would explain that the pilot had been stopped so they would not have surgery as part of KORAL. He would explain that the treatment options were now medical management or arthroscopic lavage (although the evidence for the latter was weak), and that the patient could choose between having arthroscopic lavage or medical management. One of the participants opted to proceed with surgery, subsequently underwent this surgery and was discharged from routine care. The other participant did not attend a number of clinic appointments to discuss the options, and was subsequently discharged.

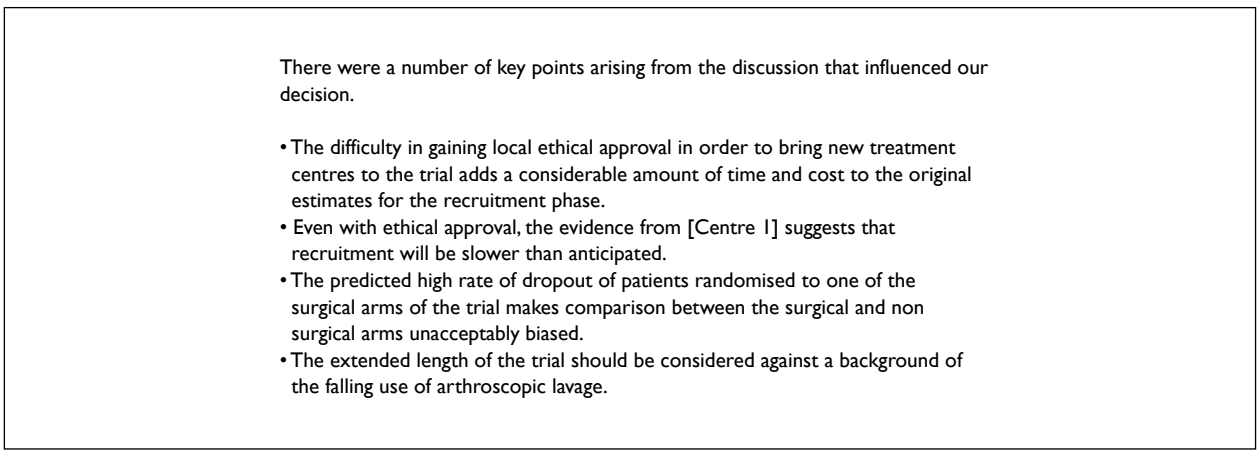

FIGURE 5 *Extract from the KORAL decision letter.*

3. *Those who had been randomised to non-surgical management.* Three participants had been randomised to non-surgical management, and this management was already under way before the decision teleconference. Because these patients were allocated to the non-surgical arm, they knew (by default) the group to which they had been allocated. They were invited to attend follow-up clinics 3 months after recruitment, as described in the pilot protocol.

Participants in all groups subsequently followed normal discharge procedures as appropriate.

Chapter 6
Discussion

The KORAL study addressed the specific issue of the role of a placebo control for the evaluation of arthroscopic lavage (with or without debridement). The research resulted in a number of new insights into arthroscopic lavage and how a placebo-controlled study of the procedure might be conducted in the UK. The study also identified some wider issues relevant to placebo-controlled trials of non-drug therapies in general (particularly placebo-controlled trials of interventional procedures), and thus allows further exploration of the circumstances in which a placebo-controlled trial should and could be mounted. We accept, however, that the numbers of participants included in some phases of the study were small and as such strong conclusions on the basis of these data are limited. Similarly our study was based within the UK NHS and involved a predominantly Caucasian population and as such the applicability of the results to different cultural and ethical frameworks is potentially limited.

Arthroscopic lavage – specific lessons from KORAL

Identification of a potential placebo-surgical technique for arthroscopic lavage

The focus groups with the surgeons indicated that agreement could be reached relatively quickly on a surgical placebo for arthroscopic lavage. The preferred placebo procedure involved three superficial incisions with no penetration of the knee capsule and was very similar to the procedure adopted by Moseley *et al.*[24] in their trial. Given the active comparator, arthroscopic lavage, it was perhaps not surprising that surgeons were relatively comfortable with a placebo procedure for this intervention, as the only outward indications of active arthroscopic lavage are the three small incisions indicating the access routes for the instruments. If the active procedure had involved a larger incision, it is reasonable to expect that consensus would have been harder to achieve. Under those circumstances, other mechanisms for masking the allocation might have been put forward more actively, for example, as in the trial of laparoscopic versus open cholecystectomy where large dressings were used to mask the procedure that had been undertaken.[76]

Clinical importance of the anaesthetic

Very early in the KORAL process the clinical importance of the anaesthetic became apparent. Whilst the surgical dimensions of the proposed placebo were relatively straightforward, the question of which form of anaesthesia to adopt was not so readily apparent. The anaesthetists in our study rejected the idea of using hypnotic agents (as in the Moseley trial), which might superficially be considered to be 'less risky' than general anaesthesia, because they were not all convinced the agents would produce adequate anaesthesia for the proposed placebo surgery, and they did not consider them to be safer than general anaesthesia. There was also a clear consensus that, if the trial proceeded, participants in both trial arms (the active and the placebo surgery) should receive the same general anaesthetic regimen. The anaesthetists favoured having each anaesthetist who participated in the trial use the form of general anaesthesia that they customarily used for a simple arthroscopic procedure, as they would have more experience with this approach and thus would be less likely to make errors when adhering to it. The wider literature on clinician learning, expertise and performance supports this stance as it suggests that the success of a procedure is directly related to the number of procedures undertaken by that individual (the so-called 'volume–outcome' relationship[77]) and his or her position on his or her individual learning curve.[78] As such, anaesthetists are more likely to have a beneficial outcome if they adopt the anaesthetic regimen with which they have most experience.

Postrandomisation withdrawals

When choosing between conducting a placebo-controlled and an 'open' trial, researchers are required to consider the implication of the choice of design on a number of factors that may affect the subsequent validity and generalisability of the results of the trial. One of the most common concerns when considering a placebo-controlled design is that the design may reduce recruitment

to the trial, as patients may be reluctant to accept the possibility of receiving the placebo treatment. The results of the KORAL pilot, however, did not support this view and showed that the majority of those approached (9/13) agreed to join the trial, and none of those who refused identified the placebo as a reason for not taking part. This finding was also echoed in the focus groups with people who had osteoarthritis, with the majority indicating that they would consider taking part in such a study. The main reason for this willingness to participate (put forward by those who were interviewed) was a perceived need from those with the disease to find out, once and for all, whether arthroscopic lavage was truly effective.

A further consideration when choosing whether to adopt a placebo-controlled design is the possibility of increased withdrawal of patients following randomisation, as patients come to terms with the reality of allocation to the placebo or a dissatisfaction with outcome borne from a belief that they have been randomised to placebo and that it has not improved symptoms. The KORAL pilot showed that whilst the majority of individuals approached were willing to consent to participate in the full pilot, withdrawal rates increased in the surgery arm after randomisation. Two out of the six patients randomised to surgery (active or placebo) withdrew postrandomisation, both citing amongst other reasons heightened anxiety about the possibility of receiving the placebo treatment (no patients withdrew from the non-surgical arm). This concurs with the findings of previous research which formally explored the effects of a placebo-controlled design on recruitment and retention rates,[79] and showed that withdrawal rates following randomisation were higher in those randomised to a placebo-controlled design than in those allocated to an open trial design. This suggests that those planning for a placebo-controlled trial need to accommodate for greater withdrawal rates in their sample size calculations, and to assess the implication of the increased withdrawal rates on the validity of their results.

Role of external data

The decision not to progress to full trial was informed not only by the direct experience of the KORAL feasibility data, but also by external national trend data available on the usage of arthroscopic lavage. At the start of the project, national HES indicated that around 34,000 procedures could be classified as arthroscopic lavages (or related therapeutic procedures). Wider trend data (see *Figure 4*) suggested a steady, albeit slow, decrease in the use of arthroscopic lavage over recent years, with a slightly faster rate of decline in usage following the publication of the Moseley trial in 2002. This external evidence was a crucial component in the decision not to progress to full trial, as any trial (especially one involving a placebo arm) would face increasing difficulties with recruitment against a background of falling use of a technique. The question of the effectiveness of arthroscopic lavage for osteoarthritis of the knee thus remains unanswered, although other (non placebo-controlled) studies are still being conducted which will add to the cumulative evidence base for the technique. Indeed, as this monograph was being written a further trial comparing arthroscopic lavage and debridement (in addition to optimised medical and physical therapy) compared with optimised medical and physical therapy alone was published,[80] showing no evidence of a benefit of arthroscopic lavage over non-surgical management.

The influence of external evidence in the decision-making process has many parallels with the role of external evidence in the decision-making processes of trial data monitoring committees (DMCs). A trial DMC meets regularly over the course of a trial and it is its responsibility to recommend whether the trial should continue according to the planned protocol or be stopped early. Whilst the DMC primarily reviews the emerging data from the specific trial, this is often augmented by evidence from other trials and other external sources. The importance placed on this extra external evidence is not uniform across all DMCs, but commentators suggest that external evidence should be routinely taken into account in the decision-making process.[81,82] A clear implication of this is that researchers must have close-down procedures worked through early in the life of a trial, allowing rapid response to any decision to terminate the study early. Pre-planning of close-down procedures was crucial to the smooth close down of the KORAL study, and it is recommended that all trialists prioritise this planning activity.

Generic issues related to placebo-controlled trials in surgery

Terminology

The research undertaken in this feasibility study highlighted the spectrum of language that has been used in the published literature to refer to an inactive control manoeuvre that

mimics the experimental (or placebo) treatment. The interviews and focus groups with health professionals and potential participants also highlighted that different words give rise to different connotations as to the motives behind the use of a placebo.

In medical research, a placebo is generally used to evaluate the efficacy of a drug or intervention whilst attempting to equalise any perceived positive effects induced through exposure to a treatment.[83] A placebo attempts to mimic the intervention under study, but has no known inherent mechanism of action such as to promote any expected benefits. An effective placebo, whilst attempting to maximise the mimic of the intervention, should also seek to minimise any potential harm to the recipient. The classic placebo used within a pharmacological research setting is the 'sugar pill' – a formulation that is manufactured to mimic the drug under study, but which has no known mechanism of action and whose ingredients have been selected to minimise any potential harm. Because of the long tradition of this type of placebo in the pharmacological research setting, the words 'placebo' and 'dummy' have become synonymous with formulations that are perceived to be completely inert and benign, despite many trials observing adverse events (e.g. gastrointestinal upsets) in those patients allocated to the placebo.

In trials of surgical interventions, however, it is harder to achieve an effective mimic that minimises potential harm to the extent of the sugar pill. Because the placebo in this setting cannot be inert, the word 'sham' has become commonplace to describe the use of a placebo procedure in this setting. The word 'sham', however, derives from the terminology of deception and is synonymous with wilful deceit (with its inherent negative connotations).[84] We found that the choice of word (sham or placebo) can lead to very different perceptions, despite the rationale behind their use being the same in both settings.

In the KORAL study, we chose to adopt the terminology of 'placebo surgery'. We chose this in an attempt to describe as accurately as possible the intention behind the procedure – i.e. to mimic the 'active' surgery being undertaken in the arthroscopic lavage arm of the trial (and hence the indirect effects of receiving surgery), whilst minimising the risk. This terminology was discussed with the potential participants in the focus groups and found to be an acceptable descriptor for the procedure.

The words 'placebo' and 'placebo effect' have also been shown to have some positive connotations in the clinical setting, as they can be used to describe the positive (but unexplained) improvement observed in a proportion of patients allocated to the placebo treatment,[83] as was observed in the Moseley trial.[24] We realise, however, that perceptions of the control technique might not have been so favourable had we used the terminology of 'sham surgery'; however, we did not want our results to be artificially skewed by the use of a term which we knew a priori to be negatively loaded.

Blinding

A particular complication of trials in surgery is that the surgeon cannot be blinded to the procedure. The surgeon and his team will always know which procedure a particular patient has received, and this can have consequences for the scientific rigour of the design and potentially for the doctor–patient relationship. The concept of the surgeon not being blinded to the allocated intervention within an RCT is not new,[85,86] and many commentators note that, for valid assessment of the outcome of the procedure, care must be taken to have objective measures by which improvement can be measured (or at least measures which do not rely on the subjective opinion of the operating surgeon).[87] In the KORAL study, the primary outcome was function as measured by the Oxford Knee Score – a patient reported outcome – and hence one that was not influenced by the operating surgeon.

With a placebo-controlled trial in surgery, however, there is an added issue of the surgeon knowing which patients have been given the placebo treatment and which have had the 'active' treatment. In the focus groups, the surgeons discussed the ethical dilemma this raised for the doctor–patient relationship, and the need to have a pre-planned script for managing the patients in the trial to avoid having to 'lie' to patients about the type of surgery they had received. In the KORAL pilot, a plan for how the surgeon would communicate with patients was developed before any patients were recruited to the pilot. The surgeon indicated to the patients prior to the operation that he or she would not be able to tell them which procedure they had undergone in theatre, but would tell them if the procedure had progressed as planned.

Both the surgeon and anaesthetist were unaware of the allocation until the patient was in theatre. This minimised the need for the health professionals

to conceal information about the allocation from the patient prior to the operation, and also allowed them to prepare for the surgery in the normal fashion. This had the added benefit of maximising the scientific rigour of the design as the recommended practice is to delay the randomisation to as close to the time of intervention as possible. The experience of the pilot study showed however, that, despite extensive pre-planning, some theatre staff expressed concerns about proceeding with a placebo surgery when confronted with the reality of the action. This suggests that researchers planning placebo-controlled trials in surgery in the future should actively develop communication plans specific for all those who might contribute to the process: surgeons, anaesthetists, theatre nurses, recovery staff, etc. This individualised approach to communication is commonly used in marketing, and recent research into the potential role of business and marketing theory in RCTs suggests that this approach is crucial to 'buy-in' to the trial from all stakeholders.[88]

Lay understanding of technical terms and informed consent

The KORAL study found that whilst most participants in the focus groups understood the role of the placebo, others found the concept somewhat confusing. This finding is consistent with other literature that has identified difficulties experienced by lay individuals in fully understanding technical terms such as randomisation and equipoise.[45] Given the perceived complexity for potential trial participants in understanding the role of placebo, the placebo-controlled trial may be a fruitful context in which to research the potential usefulness of decision aids in the consent process.[89] A decision aid is a formal tool to help people decide what course of action – in this case whether or not to participate in a placebo-controlled trial – is right for them. Decision aids attempt to spell out in a lay-friendly manner the arguments for and against each decision option, and allow the individual to attach personalised ratings for each, thus allowing the individual to build up a cumulative picture of which decision is right for him or her. In a recent study, Juraskova *et al.*[90] found that the use of a formal decision aid to help potential participants decide whether or not to take part in a breast cancer prevention trial improved understanding of the trial without provoking anxiety (although they noted that individuals still had problems understanding technical terms such as randomisation). To our knowledge, the role of formal decision aids is as yet untested in the context of a placebo-controlled trial.

Collective versus individual ethics

The experience of the KORAL pilot showed that, despite full MREC approval, the study required major discussion and negotiation at an individual centre level before local clinical approvals could be obtained. Many of the arguments raised at MREC level were raised again at local level, and the fact that ethics approval had been granted did not mean that clinicians would automatically accept that the process was ethical. This raised the issue of how the different perspectives by which individuals can view the ethics of a topic can lead to different conclusions being made. For example, the qualitative work undertaken with the health professionals and potential trial participants highlighted that there were a number of different ethical perspectives at play even in our limited setting. Some individuals adopted 'consequentialist' reasoning when considering the ethics of KORAL – they were considering the morality of the placebo by assessment of its consequences – whereas others adopted more 'deontological' reasoning (where the rightness or wrongness of the placebo was being determined by the characteristics of the placebo itself rather than the consequences of it). The tensions and disagreements raised by the adoption of these different approaches were apparent in the discussions.

Most clinicians in the UK adopt a professional code of conduct derived from the 'principlist' approach[59] to ethics – they are guided by the four principles of beneficence, non-maleficence, justice and respect for autonomy – and it was interesting to note that a number of those health professionals who adopted consequentialist reasoning when considering the ethics of the placebo within KORAL recognised that aspects of their professional codes of conduct were in tension with this.

It is important that those planning trials that involve complex ethical issues (such as placebo-controlled trials) recognise that a range of ethical perspectives are likely to be encountered when setting up a complex study over a number of sites, and that these different perspectives can influence the perceived acceptability of the intervention in those settings and may lead to delays and protracted negotiations within these sites.

Arrangements for indemnity

The KORAL study highlighted the lack of clarity that exists with regard to arrangements for indemnity (in particular for non-negligent harm) in clinical research. Our discussions with multiple agencies highlighted that the delineation of liability was not clear. Whilst the NHS institutions accept liability for negligent harm caused by the design and conduct of studies they initiate, NHS indemnity does not provide for 'no-fault' compensation for non-negligent harm.[69] It is unclear whether every clinical site participating in a trial is required separately to arrange for this or whether the Sponsor organisation is responsible for arranging this for all sites and individuals participating within the trial. For the limited case of the KORAL pilot, 'no-fault' compensation was arranged through the lead institution's insurers; however, had the pilot progressed to full trial these arrangements would have been revisited.

It would be helpful if the national arrangements for indemnity and non-negligent harm were clarified for all researchers involved in the conduct of clinical trials, particularly those trials that may involve a placebo arm, and perhaps NHS-wide indemnity procedures could be developed by the respective Health Departments.

Implications of staged-funded projects for trials units

Conditional, staged funding of trials such as KORAL, incorporating feasibility then a formal pilot, culminating in a definitive confirmatory trial, provides a flexible approach to managing the risks of a large-scale research project. It can provide protection for both the funder and research group from continued and unproductive involvement in a project that no longer has a meaningful chance of success. Such a design does, however, create extra challenges for a trials unit – particularly in integrating this type of study into a portfolio of mainly conventional, single-stage, unconditionally funded confirmatory trials.

Typically, a trials unit will have a business model that identifies its capacity – the number of trials that can be taken on at any one time given staffing and other constraints. So, despite the uncertainty within KORAL as to whether a full-scale trial would go ahead, a 'slot' had to be set aside for one in the capacity planning for CHaRT (the clinical trials unit supporting the KORAL study) at the start of the study. As we now know, KORAL did not progress to full trial, but for the 2 years whilst the feasibility and pilot phases were being conducted, the ongoing prospect of a full-scale trial was an important factor in CHaRT's decision whether to bid for further trials. In this type of situation, which is likely to become more commonplace in the future, the complexity of the decision-making process for trials units will inevitably increase (especially for trials units that have a number of 'KORAL-type' staged-funding projects in play at various stages of maturity). It is an interesting challenge for those managing trials units to weigh up the likelihood of progression of conditionally funded, staged trials such as KORAL (in which the progress of internal issues, but not the funder's response to these issues is known) against the competitiveness of supporting a 'de novo' proposal for a different trial. There is the obvious danger of not securing enough trials to sustain the trials unit, holding over too many slots for conditional staged-funded trials that do not progress to full trials, coupled with lower than anticipated success in funding conventional trials. It will be a challenge for trials units to integrate the management of the submission and conduct of pilot and full studies, in particular the staged conditionally funded trials such as KORAL.

A further major issue in conditional staged-funded designs is the increased uncertainty in the timelines for the early phases of the project, reflecting the degree of uncertainty and perhaps also the likely controversies in the trial question and design. In full-scale trials, whilst commonplace, delays tend to be both expected (occurring at established bottlenecks) and fixable (usually by simple solutions). However, in a challenging pilot like KORAL, the delays were more unpredictable and more difficult to solve. For example, it was difficult for CHaRT to speedily react and resolve an issue of refusal at a local level to proceed on the grounds that the study is not ethical, despite it having ethics committee approval. The uncertainties of roles and responsibilities this entails are awkward, and can require considerable time and diplomacy by the trials unit to achieve a resolution that enables the study to go forward at that centre.

Thus, whilst conditional staged funding is an attractive and flexible model for publicly funded trials, and may be particularly attractive for the development of more complex studies such as KORAL, integrating such designs into a mixed portfolio of conventional trials presents challenges to a trials unit. Trials units considering running these types of studies in the future should be aware of these challenges and plan for them.

When, and how, should a placebo-controlled trial be mounted in a surgical context?

The KORAL study provided a number of insights into the question of when and how a placebo-controlled trial should be mounted in a surgical setting. Commentators agree that the ethical principles appropriate to all clinical research must be satisfied as a minimum when considering the acceptability and feasibility of a placebo-controlled design. These principles are that the study must: (1) have scientific merit, (2) be acceptable to participants in terms of the risk-to-benefit ratio of participation and (3) be respectful of the autonomy of participants to determine whether they should participate.[91] The results of the qualitative component within the KORAL study showed that these three factors were raised and discussed in depth for the particular case of arthroscopic lavage. The scientific merit of the proposed study – the evaluation of the true effectiveness of arthroscopic lavage – and the need for informed consent were readily accepted. Whether the proposed study design provided an acceptable balance of risks and potential benefits for participants, however, generated much wider debate.

The discussion of an acceptable risk-to-benefit ratio in a placebo-controlled study is not straightforward. As Horng and Miller[61] argue, the risks must be considered in the context of alternative study designs to answer the research question: could an evaluation of arthroscopic lavage be conducted without the use of a placebo control and without compromising scientific rigour? In any trial of arthroscopic lavage, the subjective measure of pain is the primary outcome of interest. It is a well-recognised phenomenon that subjective outcomes are prone to bias when the allocation is known to the outcome assessor.[87] Any open trial that compared arthroscopic lavage with a control group that received no treatment or non-surgical treatment would thus have been prone to potentially biased results. This may go some way to explain the differences seen in the early studies of the effectiveness of arthroscopic lavage, where those open studies that compared arthroscopic lavage against no surgery (or non-surgical management) showed some evidence of benefit, whereas those studies that were conducted in a blinded manner showed none. This suggests that a placebo-controlled trial is most relevant in a surgical context when the primary outcome of interest is subjective (and thus prone to bias in other designs).

An additional consideration in the risk-to-benefit ratio for participants is the nature of the proposed placebo – how 'risky' the proposed placebo is perceived to be. A placebo must be able to mimic the intervention under evaluation, but must minimise the risks to those who might take part in the trial. Edwards *et al.*[92] suggest that perceptions of the acceptability of a placebo are likely to vary depending on the nature of the placebo in question. They suggest that when an active placebo is very intrusive or confers significant potential harm, participants need to display high levels of altruism to enter a trial. In the KORAL study there was consensus from all parties that, from a surgical perspective, the proposed placebo demonstrated not only high potential to mimic the active intervention but also low intrusiveness (three small skin incisions), and thus yielded high acceptability. The primary issue of concern was rather the perceived intrusiveness of the anaesthetic component of the placebo – the recommendation to have a general anaesthetic for those undergoing the placebo procedure. This raised concerns among many of the stakeholders within the study, and was the factor that caused most discussion with local decision-makers when seeking formal approval to conduct the KORAL pilot. It is interesting to note, however, that the subject experts, the anaesthetists, who contributed to our research viewed the use of a general anaesthetic in the placebo group as the option that did minimise the risk. They contended that the technique with which they would have more experience, a routine general anaesthetic, would be safer and that they would be less likely to make errors when administering it. We have discussed earlier how this assessment is borne out by the wider literature on expertise and errors.

Even when a placebo-controlled trial might be deemed to be an acceptable design, it must also be a feasible course of action. The experience of the KORAL study highlighted this issue well as, even when national approval for the study was gained, the trial faced a number of practical hurdles before it commenced. Inability to surmount any of these practical difficulties would have led directly to the failure of the study. The particular issues faced by KORAL highlighted that: (1) stakeholders in every trial centre need to be fully briefed about any proposed trial and any concerns need to be resolved prior to trial commencement; (2) arrangements need to be put in place to cover the costs of the placebo before any trial can go ahead;

and (3) appropriate indemnity arrangements need be instituted. Whilst these issues were particularly relevant to KORAL, they are not unusual and are likely to be faced by any researcher planning a placebo-controlled trial. In particular, the crucial importance of local stakeholders (those who might be affected by the research) and gatekeepers (those who give formal permission for the organisation to be involved in the research) has been outlined by a number of authors,[93,94] and the need to develop explicit recruitment and communication strategies has been identified.

These insights suggest, therefore, that the optimal place for a placebo-controlled trial in surgery is in situations in which the following conditions can be satisfied:

- Alternative designs would provide inferior (and potentially biased) results, particularly where the primary outcome is of a subjective nature and blinding cannot be sustained beyond the time of any placebo effect.
- A placebo surgical procedure and type of anaesthesia can be devised that adequately mimic the active intervention with a level of intrusiveness and risk that is acceptable to surgeons, anaesthetists, ethics committees and potential participants.
- Appropriate practical arrangements can be instituted in local centres to ensure that the delivery of such a design would be feasible.
- Sufficient numbers of potential participants (after assessment of clear descriptions and careful explanations in patient information leaflets of the advantages and disadvantages of taking part) judge for themselves that the risk-to-benefit ratio of participation is acceptable to them.
- Levels of compliance with the allocation are sufficiently high to sustain scientific rigour.

Overall conclusion

The KORAL feasibility study showed that, in principle, a placebo-controlled trial of arthroscopic lavage could be conducted in the UK, albeit with difficulty. It also showed, however, that the design remains controversial, and for some health professionals the use of placebo surgery can never be justified. It highlighted the importance of the surgeon–anaesthetist relationship in this context and how acceptance of the trial design by both parties is essential to successful participation. It also highlighted the importance of informed consent for trial participants and the strength and influence of individuals' ethical perspectives in addition to collective ethics provided by MRECs. All these factors need to be accounted for in the planning of future placebo-controlled trials.

The wider conclusion from the KORAL study is that the optimal place for a placebo-controlled trial in surgery is likely to be for situations in which the strict conditions listed above can be satisfied.

Implications for practice

- A placebo-controlled trial of arthroscopic lavage could be conducted in the UK, albeit with difficulty.
- Those conducting trials in surgery must consider the surgeon–anaesthetist partnerships when planning clinical trials, especially trials including a placebo arm.
- People taking part in, and authorising the conduct of, trials have their own individual ethical perspectives which can influence their practice (in addition to the collective ethics assessment provided by MRECs). Researchers need to be aware of these, and work with them, when planning clinical trials – especially trials involving a placebo arm.
- Terminology referring to 'placebos', 'shams', 'dummies', etc. should be investigated and then standardised across trials – each has different connotations that may influence participation.
- The importance of including clear descriptions and careful explanations in patient information leaflets was reinforced in this study. All trials should ensure that any advantages and disadvantages of participation are explained as fully as possible.
- Patient information leaflets within placebo-controlled trials should explicitly state that whilst benefit might be seen within a placebo group, the underlying mechanism proposed for the placebo has no known scientific rationale to support benefit.
- National arrangements for indemnity and non-negligent harm should be clarified for all researchers involved in the conduct of clinical trials, particularly those trials that might involve a placebo arm.
- The HTA programme should consider the routine use of staged funding (with integrated rapid decision-making) for more complex research projects.

Implications for research

- Research is required into the impact of different terminology referring to placebos (e.g. placebo, sham, dummy) on understanding the role and function of a placebo.
- Research is required into the usefulness of formal decision aids to aid participant consent in the context of a placebo-controlled trial.
- Research is required into the impact of individual versus collective ethics on the conduct of placebo-controlled trials.

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Contribution of authors

Marion Campbell (Director of Health Services Research Unit, lead methodologist) was the principal grant applicant, she led on the development of the study protocol, led the preparation of the report, was responsible for the overall conduct of the study and is guarantor of the study. Zoe Skea (study researcher, qualitative research) contributed to the development of the study design, and was responsible for the day-to-day management of the qualitative component of the study, led on the writing of the qualitative findings of the study and assisted in the wider preparation of the report. Alasdair Sutherland (Senior lecturer and Honorary Consultant in Orthopaedics, lead surgeon) contributed to the development of the study design, he also led on all surgical aspects of the trial including the conduct of focus groups and the surgical design and conduct of the pilot, led on the writing of the surgical aspects of the report and assisted in the wider preparation of the report. Brian Cuthbertson (Professor, lead anaesthetist) contributed to the development of the study design, led on all anaesthetic and other clinical aspects of the trial including the conduct of focus groups and the design of the pilot, led on the writing of clinical aspects of the report and assisted in the wider preparation of the report. Vikki Entwistle (Professor, qualitative methodology) contributed to the development of the study design, provided guidance to the qualitative component of the study, contributed to the conduct of the focus groups, and contributed to the writing of the qualitative findings of the study and the wider preparation of the report. Alison McDonald (Senior Trial Manager, trial management) contributed to the design of the study materials and to the organisation of study authorisations, co-ordinated liaison with study centres and assisted in the preparation of the report. John Norrie (CHaRT director, trialist) contributed to the design and conduct of the study, provided expert guidance on the contribution of clinical trials units to pilot studies and assisted in the preparation of the report. Robert Carlson (Senior lecturer, medical ethics) contributed to the design and conduct of the study, provided expert guidance on ethical arguments and the place of placebos within these frameworks, and contributed to the writing up of the ethics process and to the wider preparation of the report. Stephen Bridgman (Senior lecturer, local clinical leadership) contributed to the design and conduct of the pilot at a local level and contributed to the preparation of the report. The

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Appendix 1

Topic guide – focus group (surgeons)

Thanks/introductions

Purpose of focus group – acceptability of proposed trial…

Introduce yourself, where based, current surgical position

Who currently offers arthroscopic lavage?

- Yes – who gets it?
- No – have you ever done it/what changed?

AS presents the Moseley trial and bit about our study

Explore reactions to Moseley trial – should we be asking this question?

If FOR arthroscopic lavage, what would convince you to stop?

If AGAINST arthroscopic lavage, what would convince you to start?

Explore views about placebo surgery in general, in different research contexts. Is there any role for it? Trials of unproven procedures?

What about the use of placebo surgery in the context of a trial of arthroscopic lavage? Main concerns:

- surgery
- anaesthetic
- other.

Best placebo:

- one that would maximise the mimic
- one that would minimise the risks.

Explore reasons FOR taking part in a two-arm trial

Explore reasons AGAINST taking part in a two-arm trial:

- barriers
- legal or risk management issues.

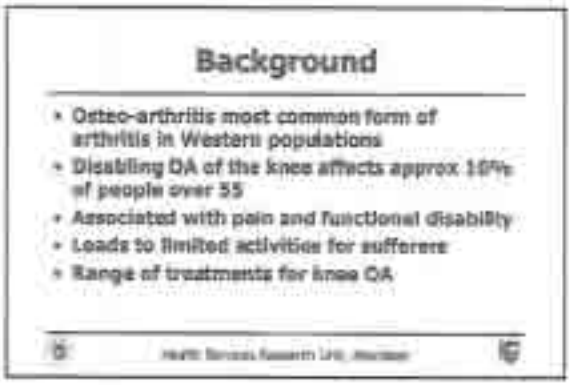
Show of hands – willing to participate as recruiting clinician/member of clinical team.

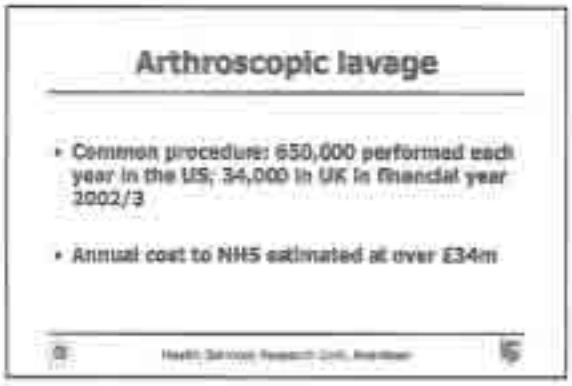
If FOR use of placebo – what would patients need to know?

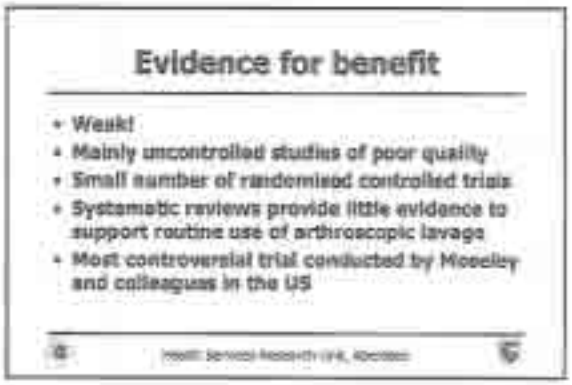
Show of hands – if you or close friend/relative had osteoarthritis, would you take part as a patient or recommend friend to take part?

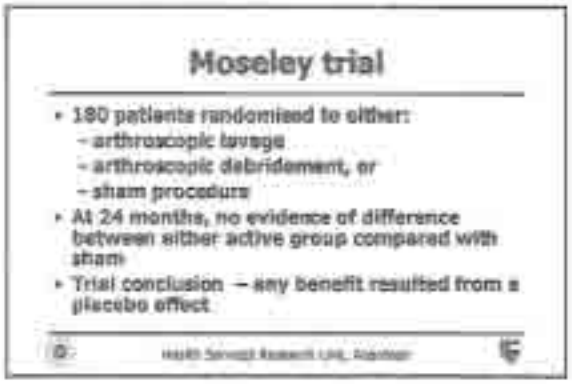
Appendix 2

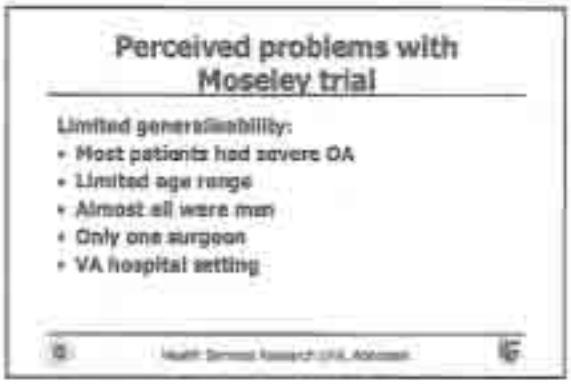
Presentation made to surgeons prior to focus group

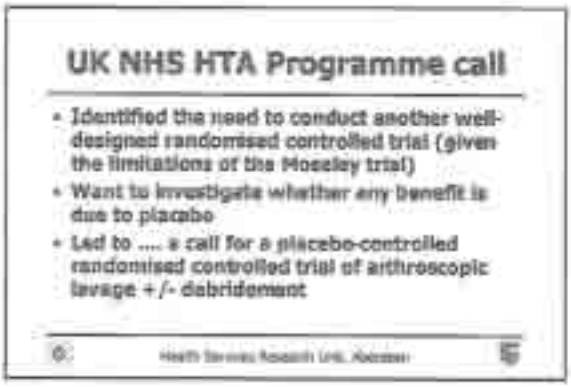


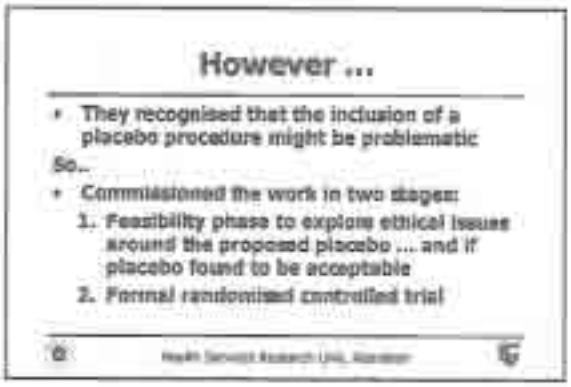


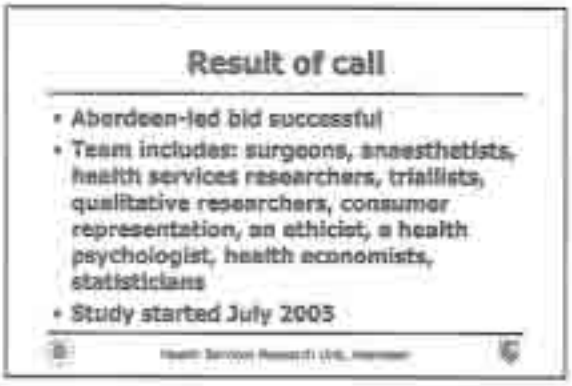


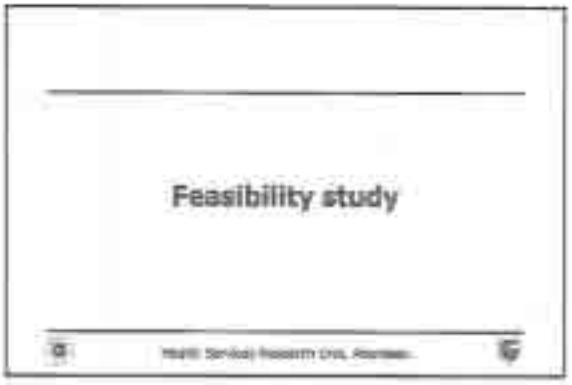





UK NHS HTA Programme call
• Identified the need to conduct another well-designed randomised controlled trial (given the limitations of the Moseley trial)
• Want to investigate whether any benefit is due to placebo
• Led to .... a call for a placebo-controlled randomised controlled trial of arthroscopic lavage +/- debridement

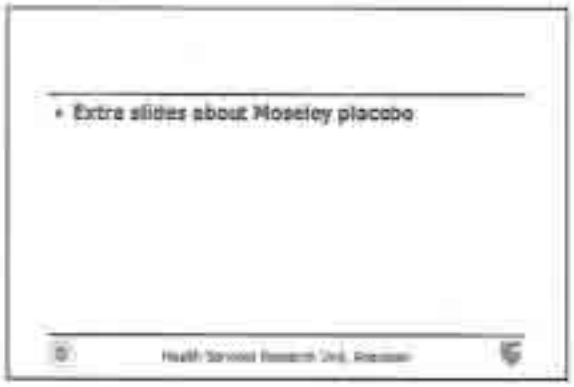

However ...
• They recognised that the inclusion of a placebo procedure might be problematic
So..
• Commissioned the work in two stages:
1. Feasibility phase to explore ethical issues around the proposed placebo ... and if placebo found to be acceptable
2. Formal randomised controlled trial

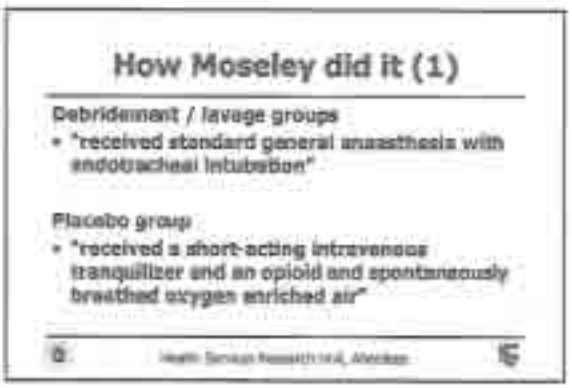

Result of call
• Aberdeen-led bid successful
• Team includes: surgeons, anaesthetists, health services researchers, triallists, qualitative researchers, consumer representation, an ethicist, a health psychologist, health economists, statisticians
• Study started July 2003

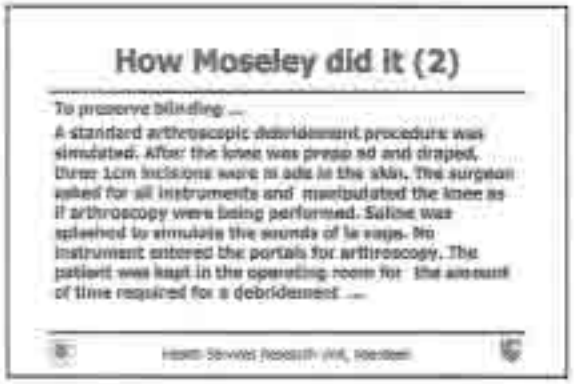

Feasibility study

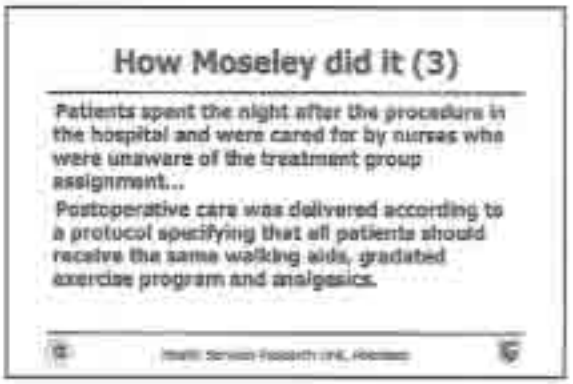

Research questions
• Which procedures might be used as 'placebos' for arthroscopic lavage?
• What do key stakeholder groups think about the use of placebo procedures in the context of a randomised controlled trial to evaluate arthroscopic lavage?


Key stakeholder groups
• Orthopaedic surgeons
• Anaesthetists
• People with osteoarthritis of the knee
• Members of research ethics committees









Appendix 3

Topic guide – focus group (anaesthetists)

Thanks/introductions

Purpose of focus group – acceptability of proposed trial …

Introduce yourself, where based, current position

Explore reactions to Moseley trial –should we be asking this question?

Explore views about placebo surgery in general, in different research contexts. Is there any role for it? Trials of unproven procedures?

What about the use of placebo surgery in the context of a trial of arthroscopic lavage? What are the main concerns:

Best placebo:

- one that would maximise the mimic
- one that would minimise the risks.

Explore reasons FOR taking part in a two-arm trial

Explore reasons AGAINST taking part in a two-arm trial:

- barriers
- legal or risk management issues.

What about modification to the basic two-equal arm trial design, e.g. a three-arm trial (is there a role for non surgical management as a control); different randomisation ratios; waiting lists rather than placebo …

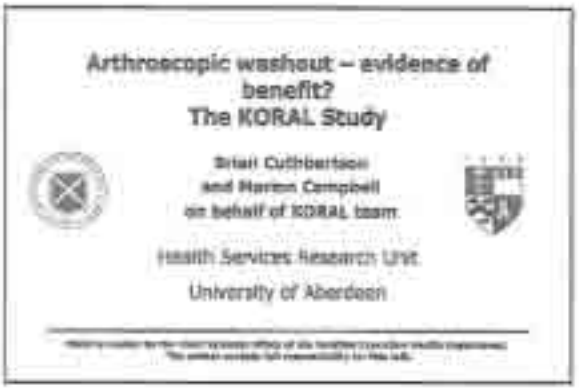
Show of hands – willing to participate as recruiting clinician/member of clinical team?

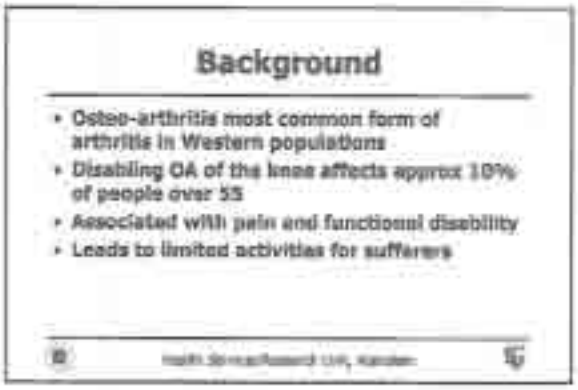
If there *is* to be some form of placebo – what would patients need to know?

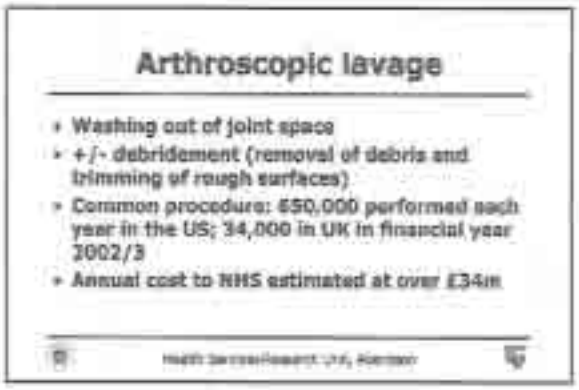
Show of hands – if you or a close friend/relative had osteoarthritis, would you take part as a patient or recommend your friend to take part?

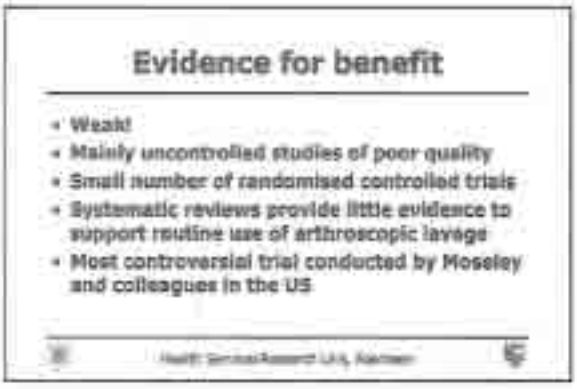
Appendix 4

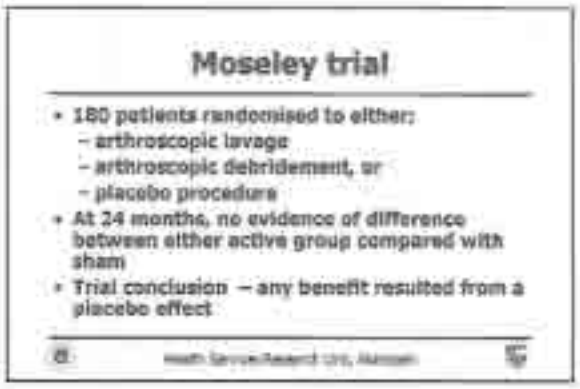
Presentation made to anaesthetists prior to focus group

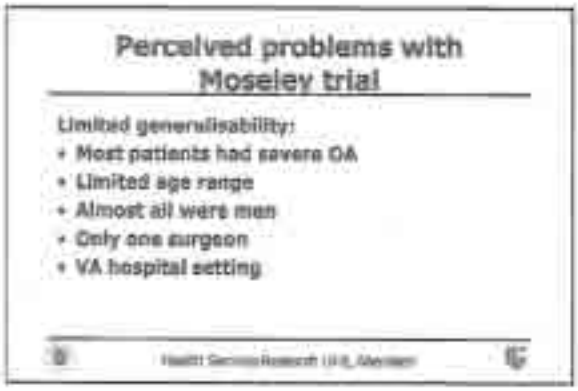


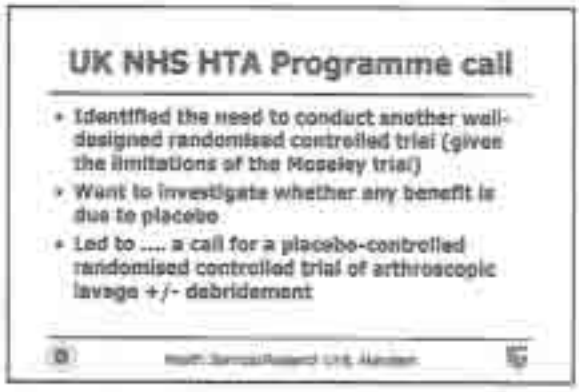









Perceived problems with Moseley trial
Limited generalisability:
• Most patients had severe OA
• Limited age range
• Almost all were men
• Only one surgeon
• VA hospital setting


UK NHS HTA Programme call
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• Want to investigate whether any benefit is due to placebo
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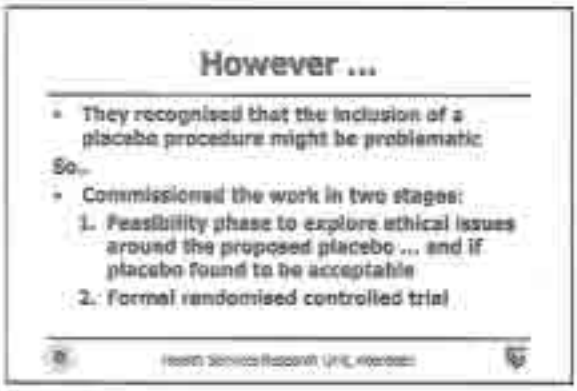
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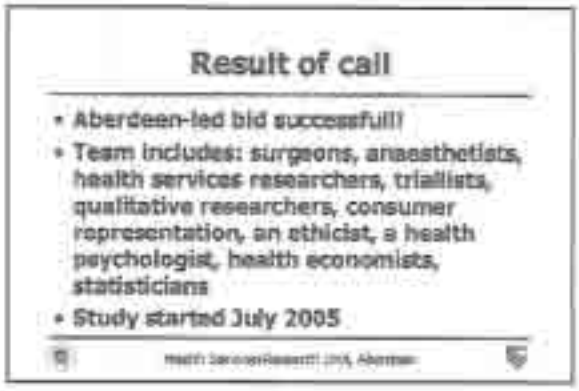
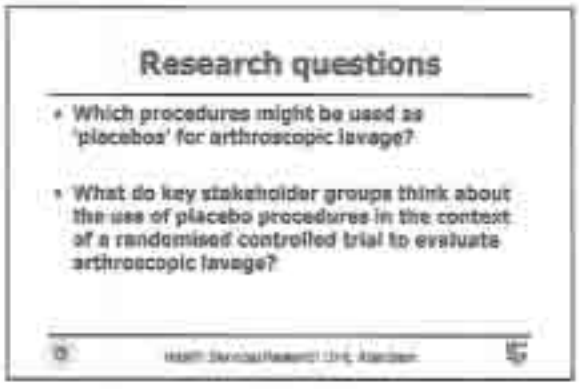
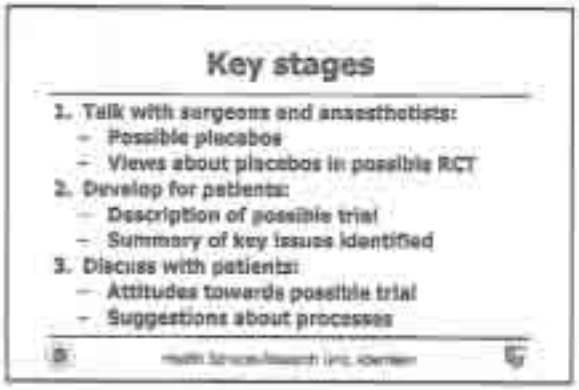
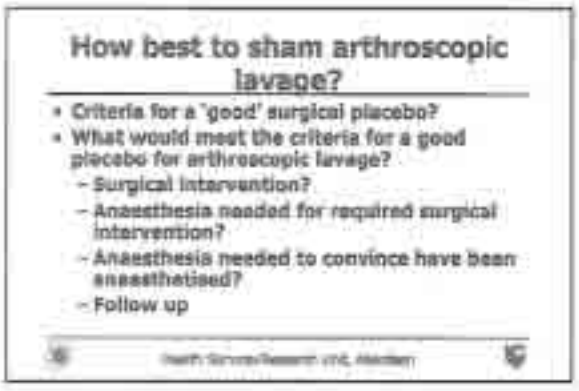
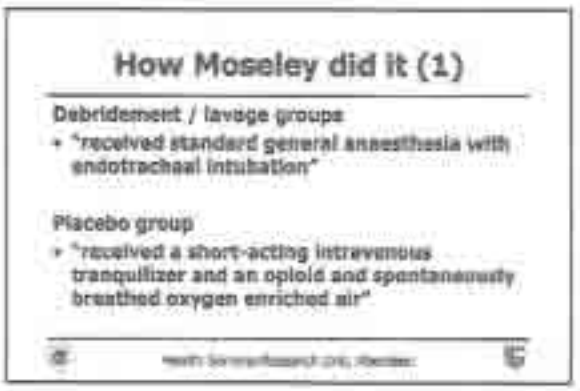

Result of call
• Aberdeen-led bid successful!
• Team includes: surgeons, anaesthetists, health services researchers, triallists, qualitative researchers, consumer representation, an ethicist, a health psychologist, health economists, statisticians
• Study started July 2005

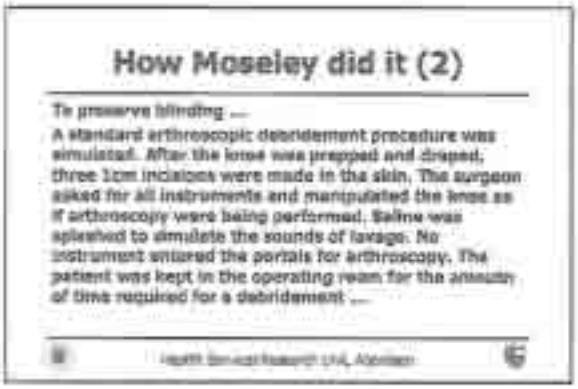

Feasibility study

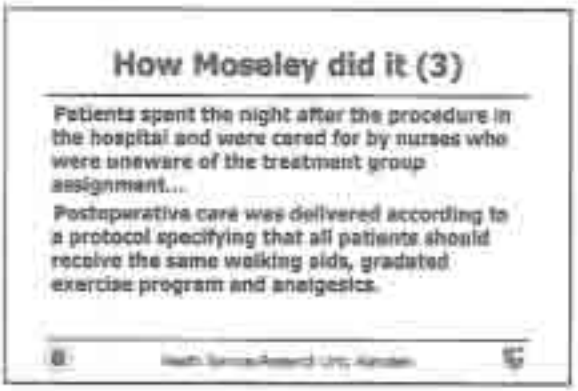

Research questions
• Which procedures might be used as 'placebos' for arthroscopic lavage?
• What do key stakeholder groups think about the use of placebo procedures in the context of a randomised controlled trial to evaluate arthroscopic lavage?








How Moseley did it (2)
To preserve blinding ...
A standard arthroscopic debridement procedure was simulated. After the knee was prepped and draped, three 1cm incisions were made in the skin. The surgeon asked for all instruments and manipulated the knee as if arthroscopy were being performed. Saline was splashed to simulate the sounds of lavage. No instrument entered the portals for arthroscopy. The patient was kept in the operating room for the amount of time required for a debridement ...


How Moseley did it (3)
Patients spent the night after the procedure in the hospital and were cared for by nurses who were unaware of the treatment group assignment...
Postoperative care was delivered according to a protocol specifying that all patients should receive the same walking aids, gradated exercise program and analgesics.


Should there be a placebo-controlled trial?
• Arguments for?
• Arguments against?
• Essential features sine qua non


Advice welcome!
• Survey of anaesthetists
– How to maximise response?
– Key questions/ways of asking?
– Willing to talk through draft?


Thank you!

Appendix 5

Topic guide – focus group (people with osteoarthritis)

Introductions

(1) If you could just start by introducing yourself, say how long you have had osteoarthritis for, and briefly describe the types of treatments you have tried already.
   - Probes – so you've mentioned X, Y and Z. Are there any other treatments available do you know of?
   - For X, Y and Z, what are your opinions about how well the different treatments work [where did you get this info from]
   - And what about problems/side effects

(2) I mentioned the trial in the US that has already investigated the effectiveness of the common procedure arthroscopic lavage for people with osteoarthritis of the knee.
   - Were you aware of this trial – if so, where did you find out about it?
   - What do you think about it?

(3) Now, I spoke about why the NHS has suggested that there should be another placebo controlled trial. I just want to put you on the spot and ask if you think you would take part in a study in which half were randomly allocated to get arthroscopic lavage and half were randomly allocated to get a placebo procedure.
   - If yes (why?)
   - If no (why?)

(4) Do you think this trial should go ahead – do you think that it is a good thing that we are proposing to do this?

Key rationales (use as probes if necessary)

Arthroscopic lavage has become a common treatment for osteoarthritis of the knee without there having been any proper scientific investigation of whether it is effective or not. (Some doctors offer it because they believe that it is effective, whereas others are more sceptical about its effectiveness and so do not offer it.)

So some people have argued that in order to improve the care of patients in the future it is important to investigate this properly, in other words, because of the uncertainty of current scientific evidence in general, i.e. a lot of the doctors that we've spoken to believe that we are attempting to answer an important question. *What do you think?*

Also, in light of this uncertainty with regard to the scientific evidence, if arthroscopic lavage is not effective, you could argue that a number of patients are currently being given an ineffective treatment.

Conversely, if it is an effective treatment then you could argue that some patients are being denied an effective treatment by doctors who do not currently offer it?

What do you think about these arguments?

(5) What about the problems related to trying to conduct this kind of trial?

Key ethical issues

Some people have argued that doctors should not expose patients to risks (in the case of this trial, there would be a risk from the general anaesthetic if there is no prospect of possible benefits).

Patient recruitment – would patients take part

What do you think?

(6) What kinds of things would have to be put in place to make a trial like this acceptable?

(7) OK, imagine you were approached to take part, what would be the potential advantages of you taking part? What about the potential disadvantages?

(8) Obviously we want to make the proposed trial 'as good as possible' for participants – would any modifications/changes to the nature of the placebo surgery make any difference to whether or not people would be willing to take part? As I mentioned, we've already spoken with surgeons and anaesthetists and there was a general consensus that the placebo group should receive two/three superficial cuts to the knee about that all should receive a general

anaesthetic. The main reason for this was the need to standardise as much as possible across the groups.

- What about the study design. What about if instead of half getting the placebo and half the arthroscopic lavage, what if there was an extra group who would get given, say physiotherapy (so patients had only a one in three chance of getting the placebo surgery)…would any of that make a difference?
- What if we got rid of the placebo group altogether and we had say one group that got arthroscopic lavage and another group who were simply put on a waiting list. This would mean that for our trial the waiting list would act as a control group and we could compare the two groups in order to see if arthroscopic lavage was effective or not?

Try and sum up.

[quick break] I have a draft of a possible patient info leaflet about the trial (the kind of one that might go out to people when we are trying to recruit them) and what we'll do is take a quick break and I'll let you have a look over this and then we'll start the tape and just go through it if that's OK.

OK, so you've had a look at the leaflet.

(9) What do you think about it?
- Do you think it covers what people would need to know before they can decide whether or not to take part?
- What bits should be kept?
- What should be deleted?
- What should be added?
- Anything that could be worded better?

(10) Is there anything else that you'd like to say in relation to this trial?

Appendix 6

Draft information leaflet about proposed trial

KORAL

KNEE OSTEOARTHRITIS:
ROLE OF ARTHROSCOPIC LAVAGE

PATIENT INFORMATION LEAFLET

The KORAL study is funded by the UK NHS R&D Health Technology Assessment Programme

What is osteoarthritis of the knee?

Osteoarthritis (OA) is a disease that affects the joints in the body. 'Osteo' means bone and 'arthritis' means joint damage and swelling (inflammation). When joints are swollen and damaged they can be painful and can affect mobility. Osteoarthritis of the knee is a very common form of osteoarthritis.

How can osteoarthritis of the knee be treated?

There are a range of treatments available for people have OA of the knee. These include painkillers (such as paracetamol), anti-inflammatory drugs or creams, steroid injections, and surgery. Sometimes, 'keyhole' surgery techniques are used to 'wash out' loose fragments of bone and other tissue from the joint. This is called arthroscopic lavage. Sometimes, during a lavage, additional procedures may be carried out – such as smoothing the surfaces of the joint, removing flaps of damaged hard cartilage, or trimming of torn soft cartilage. This is called debridement. These techniques may offer pain relief in the early stages of OA, but previous studies do not tell us if these surgery techniques really work.

Introduction to the study

You are being invited to take part in a research study that aims to find out if arthroscopic lavage for osteoarthritis really works. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the enclosed information carefully and discuss it with your family, friends or General Practitioner if you wish. Do not hesitate to contact us if there is anything you do not understand or if you would like more information. Please take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to find out if arthroscopic lavage or debridement is an effective treatment for people with OA of the knee. In this study, doctors, researchers and patient representatives are working together to compare three options against each other:

- 'arthroscopic lavage'
- 'placebo' procedure (simulated surgery)
- Management without surgery (e.g. physiotherapy).

What treatment will I receive?

If you agree to take part in the study, your type of treatment will be chosen randomly by a computer. You will not know which treatment group you are in if you are allocated to receive either 'arthroscopic lavage' or the 'placebo' procedure (simulated surgery). You will have a one in three chance of receiving either:

1. Arthroscopic lavage
If you are allocated to this group you will receive arthroscopic lavage (with some debridement if your surgeon thinks it is necessary). Arthroscopic lavage is a 'keyhole' surgery technique. A small camera will be inserted into your knee to allow the surgeon to see. The surgeon will then 'wash out' any loose fragments of bone and other tissue from the joint. Debridement involves smoothing the surfaces of the joint, removing any flaps of damaged hard cartilage, and trimming torn soft cartilage. This procedure would not usually require an overnight stay in hospital but approximately 2 to 3 days off work (depending on nature of work). This procedure requires a general anaesthetic.

2. 'Placebo' procedure (simulated surgery)
If you are allocated to this group you will receive a 'placebo' procedure. Placebo, or dummy, tablets are regularly used in studies to evaluate new medicines. This study will use a surgical placebo. Placebo surgery simulates or mimics a surgical procedure, but the person allocated to receive it does not actually undergo the full surgical procedure.
If you are allocated to this group, your surgeon will make three very small incisions in the skin on your knee. No instrument would be inserted into your knee. These incisions would be very similar to the ones given to people in the 'arthroscopic lavage' group, but they would not be as deep. This procedure would not usually require an overnight stay in hospital but approximately 2 to 3 days off work (depending on nature of work). This procedure requires a general anaesthetic.

3. Management without surgery
If you are allocated to this group, you will not receive any surgery. Instead, the surgeon responsible for your care will recommend the standard form of treatment such as, for example, physiotherapy.

What will I be asked to do if I take part?
If you agree to take part in this study you will be randomly allocated to receive one of the three treatments. The treatment will be given by the same doctors and nurses who would treat you if you were not taking part. You will then be followed-up at 6, 12 and 24 months. You will sent a questionnaire which will ask about any pain in your knee, your general health and any visits you have had to the GP or hospital about your knee arthritis.

Why have I been approached?
This hospital is one of several centres throughout the UK taking part in this study. As a person currently receiving care for OA of the knee, you may be eligible to take part in the study. We plan to involve about 500 patients who have OA of the knee throughout the UK.

What are the advantages and disadvantages of taking part?
Advantages
The treatments, including the placebo procedure, may offer some relief from the painful symptoms of early OA of the knee. A similar study carried out on a small scale in the US has found that all treatments offered some benefit (Moseley 2002). The information we get from this study may help us to provide better treatment in the future for patients with OA of the knee.

Disadvantages
The disadvantages of either surgical operation (arthroscopic lavage or the placebo procedure) are:
- it requires approximately 2 to 3 days off work (depending on nature of work)
- as with all surgery that involves a general anaesthetic, there is a risk, albeit a very low risk, of serious complications or operative death.

We want to reassure you that:
- Your involvement in the study is entirely voluntary.
- You are free to withdraw at any time and this would not affect your current or future medical treatment. Although we do not expect participation to affect private medical insurance, if you have insurance, please check with the company before agreeing to take part in the study.
- All information collected for the study will be treated as confidential and used only for the purpose of the study.
- We will inform your GP that you are taking part.
- All people taking part will be kept informed about the study and will be sent a summary of the results. The results of the study will be published in medical journals. Participants will not be identifiable in any of the study reports.
- This study has been approved by all the appropriate agencies.
- This study is being undertaken on behalf of the NHS.
- This study is being developed with full collaboration of Arthritis Care.

What if something goes wrong?

In the very unlikely event that you are harmed by taking part in this study, there are special insurance arrangements being put in place.

Who is organising and funding the research?

The study is funded by the Department of Health Research and Development Health Technology Assessment Programme. A team based in Aberdeen is responsible for the day to day management of the study. However, this hospital is one of several throughout the UK taking part and your doctor is part of the collaborating team.

Thank you for reading this

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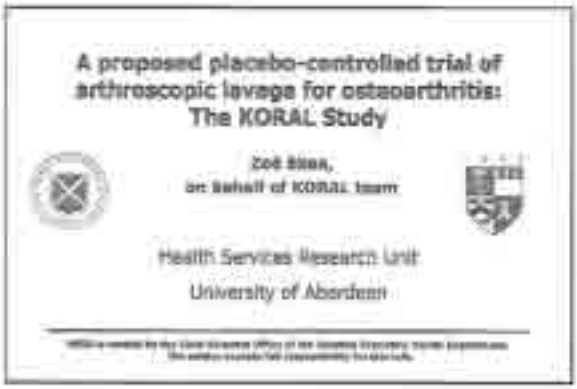
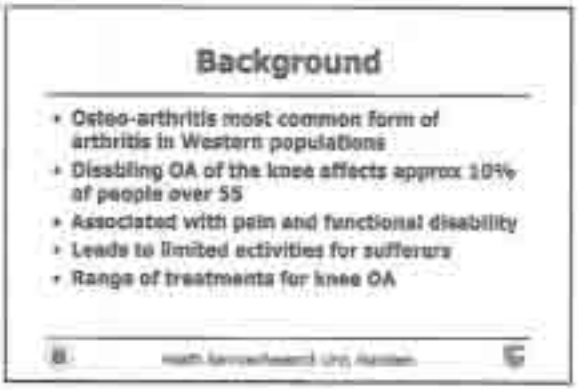
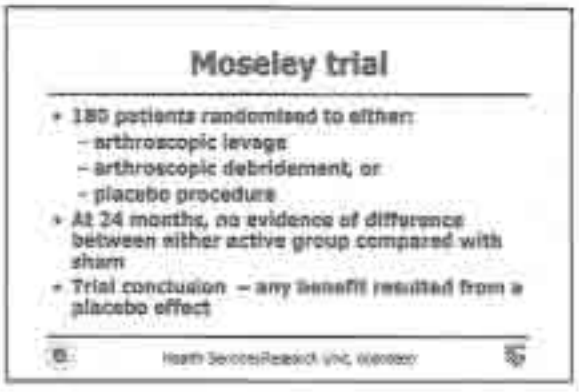
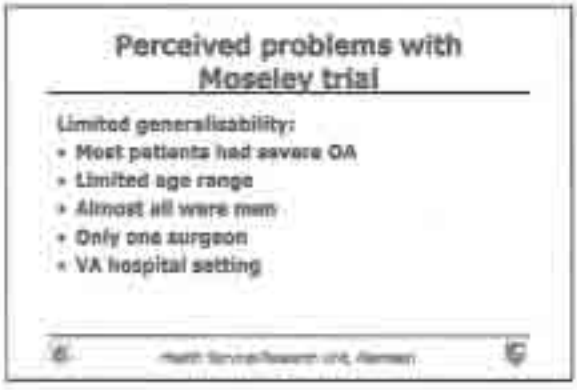
Appendix 7

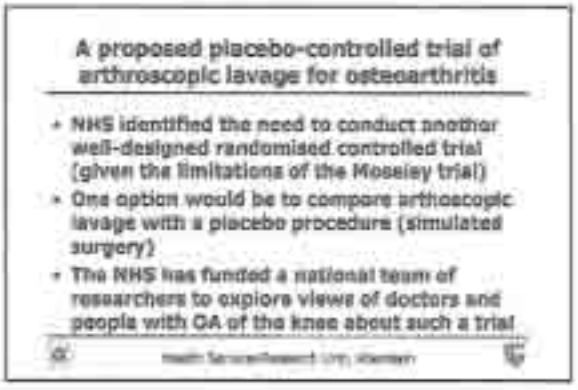
Presentation made to people with osteoarthritis prior to focus group

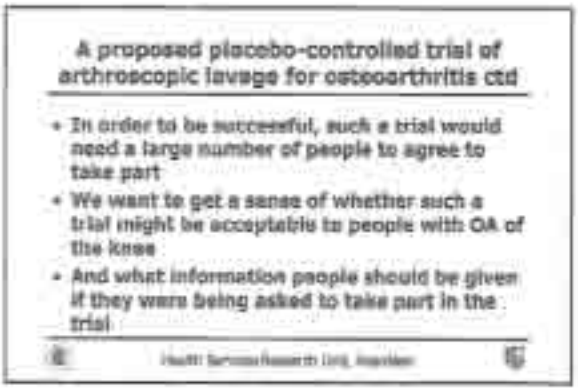











A proposed placebo-controlled trial of arthroscopic lavage for osteoarthritis ctd
• In order to be successful, such a trial would need a large number of people to agree to take part
• We want to get a sense of whether such a trial might be acceptable to people with OA of the knee
• And what information people should be given if they were being asked to take part in the trial


•What do you think?

Appendix 8

Topic guide – MREC interviews

(1) Quick summary of proposed trial and preliminary findings from discussions that we've already had with surgeons/anaesthetists/patients.
(2) Ask chairperson to introduce themselves and say a bit about role within their MREC.
(3) Thinking about our proposed trial, based on the written information that you have received along with my brief summary, what are your initial thoughts about it from an ethical perspective?

Probes:

- Arthroscopic lavage has become a common treatment without there having been any proper scientific investigation of whether it is effective or not. So, because of the uncertainty of current scientific evidence, several of the health professionals that we've talked with believe we are attempting to answer an important question. What do you think?
- What about the argument that surgical procedures of unproven benefit that are currently in routine use also pose a risk to patients?
- Some people have argued that placebo controls are especially appropriate for the evaluation of surgical innovation that has not previously been associated with robust scientific validation and where subjective symptoms of the patient are relied upon as outcome measures. What do you think?

(4) What do you think about the nature of the placebo we are proposing (two/three superficial cuts, no scope used, general anaesthetic given)? Would any modifications to this make it more or less acceptable from an ethical standpoint?
(5) What about the nature of the trial design that we are proposing (one in three chance of receiving: arthroscopic lavage, placebo or management without surgery)? Would any modifications to this make it more or less acceptable from an ethical standpoint?
(6) What criteria would a trial that included simulated surgery need to satisfy to be ethically acceptable?
(7) What about patient information material? What would patients need to be told from the point of view of MRECs if they were approached to take part?

Appendix 9

Survey to surgeons and anaesthetists

KORAL
KNEE OSTEOARTHRITIS
ROLE OF ARTHROSCOPIC LAVAGE

PLACEBO SURGERY: AN NHS-FUNDED TRIAL?

What do you as a surgeon think?

- The benefits of arthroscopic lavage (and/or debridement) for the management of knee osteoarthritis are unproven[1].
- The NHS is considering funding a clinical trial to assess the effectiveness of arthroscopic lavage.
- They are considering including a placebo arm within the trial.
- The possibility of a placebo has been discussed with groups of surgeons, anaesthetists, patients and ethics committee representatives.
- Informed by these discussions, the following placebo is being proposed:
  - General anaesthetic (as for arthroscopic lavage)
  - Three small skin incisions penetrating only the epidermis
  - No penetration of the knee space
- Arthroscopic lavage, placebo surgery and conservative management will be compared in terms of knee function, pain and quality of life.
- Our research group has been commissioned to find out what surgeons think of this, specifically:
  - Do <u>you</u> think the NHS should proceed with this trial?
  - What are <u>your</u> views on the plan for the trial?
  - Would <u>you</u> take part?
- Please take the time (approx. 2 minutes) to complete this questionnaire.
- The results of this survey will <u>directly</u> influence whether this trial will be conducted.

Q1. If a trial of **arthroscopic lavage** vs **placebo surgery** vs **conservative management** were to be funded in the UK:

a) would you be supportive of such research being mounted? Yes ☐ No ☐

b) would you consider taking part? Yes ☐ No ☐

c) if a friend or member of your family had osteoarthritis of the knee and were asked to participate in this trial would you encourage them to sign up for the trial? Yes ☐ No ☐

[1] Bandolier: Surgery for arthritic knee: roundup (2002). http://www.jr2.ox.ac.uk/bandolier/booth/Arthritis/arthrokn.html

Q2. If a trial of **arthroscopic lavage** versus **conservative management** only (ie **no placebo**) were funded in the UK:

a) would you be supportive of such research being mounted? Yes ☐ No ☐

b) would you consider taking part? Yes ☐ No ☐

c) If a friend or member of your family had osteoarthritis of the knee and were asked to participate in this trial would you encourage them to sign up for the trial? Yes ☐ No ☐

Q3. If a placebo trial went ahead the randomisation between groups could be made **equal** (ie equal chance of allocation to arthroscopic lavage, placebo surgery, or conservative management) or **unequal** (ie randomisation loaded to favour allocation to active surgery). What do you think would be the best strategy?

Equal randomisation (1:1:1 allocation to arthroscopic lavage, placebo surgery, conservative management) ☐

Unequal randomisation (2:1:1 allocation to arthroscopic lavage, placebo surgery, conservative management) ☐

No preference ☐

Other randomisation ratio (please specify) _____

Q4. Do you currently perform arthroscopic lavage (and/or debridement) for the management of knee osteoarthritis?

Yes ☐

I used to, but not now ☐

No ☐

If you used to perform arthroscopic lavage but do not now, why did you stop?

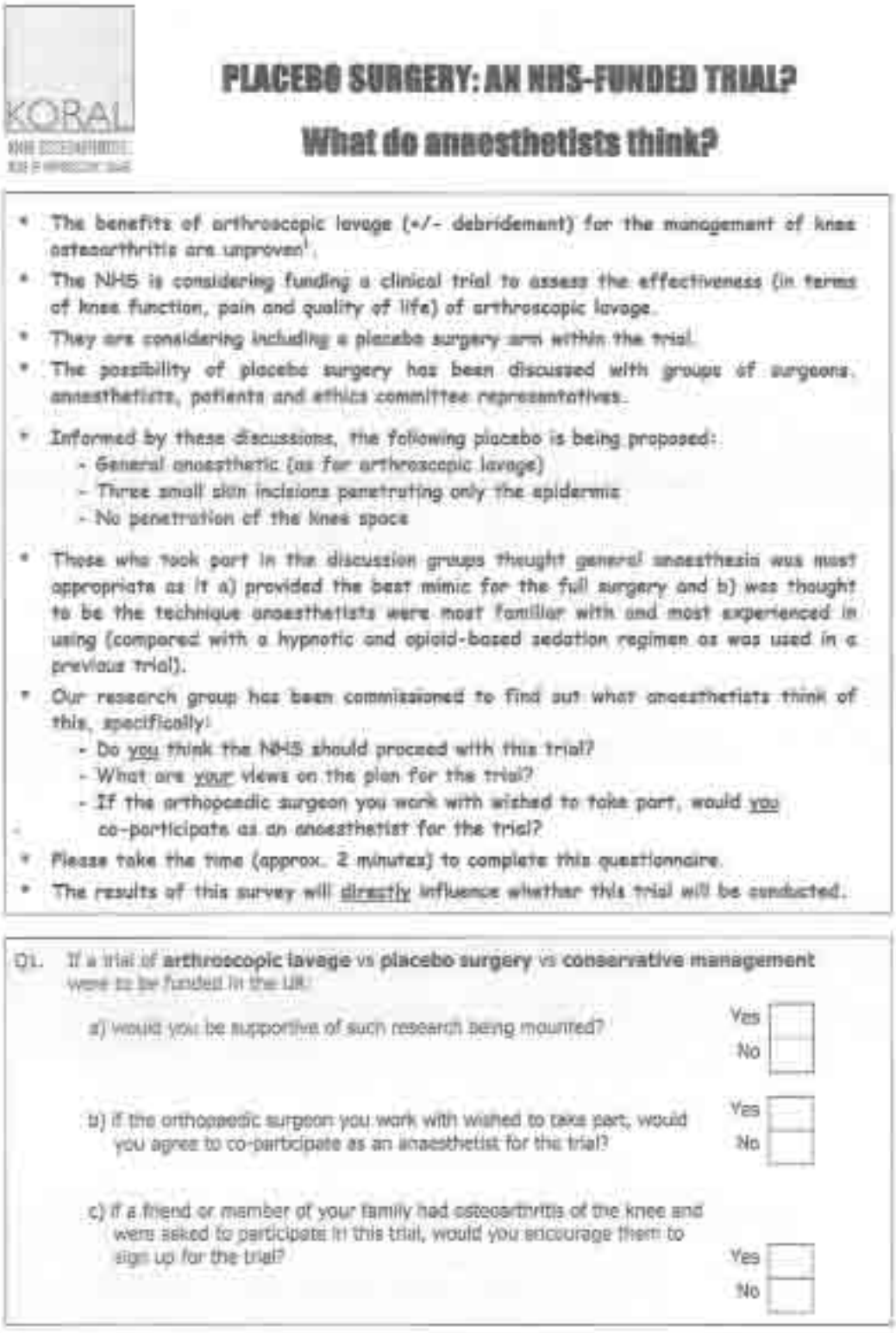
(please specify): _____

Q5. Do you have any other comments to make about this proposed research?

(please use an additional sheet if required)

Thank you for completing this questionnaire

Please return it in the envelope provided



KORAL

PLACEBO SURGERY: AN NHS-FUNDED TRIAL?

What do anaesthetists think?

- The benefits of arthroscopic lavage (+/- debridement) for the management of knee osteoarthritis are unproven[1].
- The NHS is considering funding a clinical trial to assess the effectiveness (in terms of knee function, pain and quality of life) of arthroscopic lavage.
- They are considering including a placebo surgery arm within the trial.
- The possibility of placebo surgery has been discussed with groups of surgeons, anaesthetists, patients and ethics committee representatives.
- Informed by these discussions, the following placebo is being proposed:
  - General anaesthetic (as for arthroscopic lavage)
  - Three small skin incisions penetrating only the epidermis
  - No penetration of the knee space
- Those who took part in the discussion groups thought general anaesthesia was most appropriate as it a) provided the best mimic for the full surgery and b) was thought to be the technique anaesthetists were most familiar with and most experienced in using (compared with a hypnotic and opioid-based sedation regimen as was used in a previous trial).
- Our research group has been commissioned to find out what anaesthetists think of this, specifically:
  - Do you think the NHS should proceed with this trial?
  - What are your views on the plan for the trial?
  - If the orthopaedic surgeon you work with wished to take part, would you co-participate as an anaesthetist for the trial?
- Please take the time (approx. 2 minutes) to complete this questionnaire.
- The results of this survey will directly influence whether this trial will be conducted.

Q1. If a trial of **arthroscopic lavage** vs **placebo surgery** vs **conservative management** were to be funded in the UK:

a) would you be supportive of such research being mounted? Yes ☐ No ☐

b) if the orthopaedic surgeon you work with wished to take part, would you agree to co-participate as an anaesthetist for the trial? Yes ☐ No ☐

c) if a friend or member of your family had osteoarthritis of the knee and were asked to participate in this trial, would you encourage them to sign up for the trial? Yes ☐ No ☐

Q2. If a trial of **arthroscopic lavage** versus **conservative management** only (ie **no placebo**) were funded in the UK:

a) would you be supportive of such research being mounted? Yes ☐ No ☐

b) if the orthopaedic surgeon you work with wished to take part, would you agree to co-participate as an anaesthetist for the trial? Yes ☐ No ☐

c) if a friend or member of your family had osteoarthritis of the knee and were asked to participate in this trial, would you encourage them to sign up for the trial? Yes ☐ No ☐

Q3. If a placebo trial went ahead the randomisation between groups could be made **equal** (ie equal chance of allocation to arthroscopic lavage, placebo surgery, or conservative management) or **unequal** (ie randomisation loaded to favour allocation to active surgery). What do you think would be the best strategy?

Equal randomisation (1:1:1 allocation to arthroscopic lavage, placebo surgery, conservative management) ☐

Unequal randomisation (2:1:1 allocation to arthroscopic lavage, placebo surgery, conservative management) ☐

No preference ☐

Other randomisation ratio (please specify) _____

Q4. Do you have any other comments to make about this proposed research?
(please use an additional sheet if required)

Thank you for completing this questionnaire
Please return it in the envelope provided

Appendix 10

Patient information leaflet (parts 1 and 2)

Part 1

KORAL

KNEE OSTEOARTHRITIS:
ROLE OF ARTHROSCOPIC LAVAGE

Part 1:
Why is this study being conducted?

PATIENT INFORMATION LEAFLET
PHASE 2: PILOT STUDY

Version 3, January 2007
ISRCTN81213876

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Part 1 tells you the purpose of this study. Part 2 gives you more detailed information about what would happen if you took part. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The KORAL study is funded by the UK NHS R&D Health Technology Assessment Programme

Osteoarthritis (OA) is a disease that affects the joints in the body. When joints are swollen and damaged they can be painful and can affect mobility. Osteoarthritis of the knee is a very common form of the disease. There are a number of treatments available for people who have OA of the knee. These include painkillers (such as paracetamol), anti-inflammatory drugs or creams, steroid injections, physiotherapy and surgery.

Sometimes, 'keyhole' surgery techniques are used to 'wash out' loose fragments of bone and other tissue from the joint. This is called **arthroscopic lavage**. Sometimes, additional procedures may be carried out – such as smoothing the surfaces of the joint, removing flaps of damaged hard cartilage, and trimming torn soft cartilage. This is called **debridement**. These surgical techniques may offer pain relief in the early stages of OA, but doctors and researchers are not sure if these surgical techniques are very effective.

"Clinical trials" are a recognised way of finding out if treatments are effective. The NHS is keen to run a clinical trial to find out if arthroscopic lavage (with or without debridement) is effective. One option that has been suggested is a trial that would compare 'arthroscopic lavage' against a 'placebo' procedure (simulated surgery). Placebo surgery simulates or mimics a surgical procedure, but the person does not actually undergo the full surgical procedure. The NHS has funded a national team of researchers to explore whether such a trial could be undertaken. In order to be successful, such a trial would need a large number of people to agree to take part. We have already had extensive discussions with surgeons, anaesthetists and other people like you who have knee osteoarthritis to help us decide what the trial might look like.

Why have I been approached?

Your hospital is taking part in this pilot study. As a person currently receiving care for OA of the knee, you may be eligible to take part in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. We will describe the study to you, go through this information sheet and answer any questions you may have. You will be given a copy of this information sheet to keep. If you are eligible and agree to take part, we will then ask you to sign a consent form. If you decide not to take part, this will not affect the standard of care you receive. You do not have to give a reason if you decide not to take part, but as this is a pilot study, it would be very helpful for researchers to know your reasons why.

What will I be asked to do if I take part?

If you agree to take part in this pilot study you will receive one of three procedures: 1) Arthroscopic lavage; 2) Simulated arthroscopic lavage ('placebo' procedure); or 3) Specialist re-assessment and non-surgical management (eg drugs or creams, physiotherapy or steroid injections).

Your procedure will be chosen 'randomly' by a computer. You will not know which group you are in. If you are allocated to receive either 'arthroscopic lavage' or 'simulated arthroscopic lavage (the 'placebo' procedure). The treatment will be given by the same doctors and nurses who would treat you if you were not taking part. You will then be followed-up at 3, 6, 12 and 24 months. We will send you a questionnaire from the KORAL study office in Aberdeen asking about any pain in your knee, your general health and any visits you have had to the GP or hospital about your knee arthritis.

What will happen to me if I take part?

If you agree to take part, you have a one in three chance of receiving one of the following three procedures:

1. **Arthroscopic lavage**
   Arthroscopic lavage is a 'keyhole' surgery technique. Three incisions will be made in your knee. A small camera will be inserted into your knee to allow the surgeon to see. The surgeon will then 'wash out' any loose fragments of bone and other tissue from the joint. If necessary, the surgeon will also carry out 'debridement', which involves smoothing the surfaces of the joint, removing any flaps of damaged hard cartilage, and trimming torn soft cartilage. This procedure would not usually require an overnight stay in hospital, but usually requires approximately 2 to 3 days off work (depending on the nature of your work). ***This procedure requires a general anaesthetic.***

2. **'Simulated' arthroscopic lavage ('placebo' procedure)**
   This study will use a surgical placebo. Placebo surgery simulates or mimics a surgical procedure, but the person does not actually undergo full arthroscopic lavage. Your surgeon will make three very small incisions in the skin on your knee. These incisions would be very similar to the ones given to people in the 'arthroscopic lavage' group, but they would not be as deep. No instrument will be inserted into your knee. This procedure would not usually require an overnight stay in hospital but usually requires approximately 2 to 3 days off work (depending on the nature of your work). ***This procedure requires a general anaesthetic.***

3. **Specialist re-assessment and non-surgical management (eg drugs or creams, physiotherapy, or steroid injections)**
   If you are allocated to this group, you will not receive any surgery. Instead, you will have a specialist re-assessment of your condition with the consultant surgeon responsible for your care. (S)he might recommend a number of treatments eg physiotherapy or injection depending on your symptoms.

What are the advantages and disadvantages of taking part?

Advantages

The information we get from this study may help us to provide better treatment in the future for patients with osteoarthritis of the knee. However, taking part will not necessarily help your osteoarthritis. The procedures, including the placebo procedure, may offer some relief from the painful symptoms of early OA of the knee. A similar study carried out with a small number of participants in the USA found that all procedures offered some benefit. However, it should be noted that any relief from pain experienced by those allocated to the placebo group will be due to what is known as a 'placebo effect'. This is where people in the placebo group may improve solely because they think they have received an active treatment.

Disadvantages

The disadvantages of taking part are that:

- the 'placebo' procedure is not designed to improve symptoms
- 2 to 3 days off work (depending on nature of your work) are required for surgery
- there is the potential for some post-operative pain with the surgical procedure
- as with all surgery that involves a general anaesthetic, there is a risk, albeit a very low risk, of serious complications or operative death.

What treatment options will be available for me if I decide not to take part?
A decision not to take part in this study will not affect the standard of care you receive. There are a range of treatments available for people who have OA of the knee. Your doctor will discuss the range of treatments available to you in your hospital.

We want to reassure you that:
- Your involvement in the study is entirely voluntary.
- You are free to withdraw at any time and this would not affect your current or future medical treatment.
- Although we do not expect participation to affect private medical insurance, if you have insurance, please check with the company before agreeing to take part in the study.
- All information collected for the study will be treated as confidential and used only for the purpose of the study.
- We will inform your GP that you are taking part.
- All people taking part will be kept informed about the study and will be sent a summary of the results if they wish. The results of the study will be published in medical journals. Participants will not be identifiable in any of the study reports.
- This study has been approved by all the appropriate agencies.
- This study is being undertaken on behalf of the NHS.
- This study is being developed with full collaboration of Arthritis Care.

What if something goes wrong?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information about this is given in Part 2 of this leaflet.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2 of this leaflet.

If the information in this leaflet has interested you and you are considering participation, please read the additional information in Part 2 of this leaflet before making any decision.

Thank you for reading this

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Local details

Clinical lead:

Recruitment Officer:

Part 2

KORAL

KNEE OSTEOARTHRITIS:
ROLE OF ARTHROSCOPIC LAVAGE

Part 2:
What will happen if I take part?

PATIENT INFORMATION LEAFLET
PHASE 2: PILOT STUDY

Version 3, January 2007
ISRCTN[illegible]

The KORAL study is funded by the UK NHS R&D Health Technology Assessment Programme

What will I be asked to do if I take part?

As indicated in part 1 of this patient information leaflet, if you agree to take part in the pilot study you will receive one of three procedures: 1) Arthroscopic lavage; 2) Simulated arthroscopic lavage ('placebo' procedure); or 3) Specialist re-assessment and non-surgical management (eg drugs or creams, physiotherapy or steroid injections).

Your procedure will be chosen 'randomly' by a computer. You will not know which group you are in. If you are allocated to receive either 'arthroscopic lavage' or simulated arthroscopic lavage (the 'placebo' procedure). The treatment will be given by the same doctors and nurses who would treat you if you were not taking part. You will then be followed up at 2, 6, 12 and 24 months. We will send you a questionnaire from the ICORAK study office in Aberdeen asking about any pain in your knee, your general health and any visits you have had to the GP or hospital about your knee arthritis.

What will happen to me if I take part?

If you agree to take part, you have a one in three chance of receiving one of the following three procedures:

1. Arthroscopic lavage

Arthroscopic lavage is a 'keyhole' surgery technique. Three incisions will be made in your knee. A small camera will be inserted into your knee to allow the surgeon to see. The surgeon will then 'wash out' any loose fragments of bone and other tissue from the joint. If necessary, the surgeon will also carry out 'debridement', which involves smoothing the surface of the joint, removing any flaps of damaged hard cartilage, and trimming torn soft cartilage. This procedure would not usually require an overnight stay in hospital, but usually requires approximately 2 to 3 days off work (depending on the nature of your work). ***This procedure requires a general anaesthetic.***

2. 'Simulated' arthroscopic lavage ('placebo' procedure)

This study will use a surgical placebo. Placebo surgery simulates or mimics a surgical procedure, but the person does not actually undergo full arthroscopic lavage. Your surgeon will make three very small incisions in the skin on your knee. These incisions would be very similar to the ones given to people in the 'arthroscopic lavage' group, but they would not be as deep. No instrument will be inserted into your knee. This procedure would not usually require an overnight stay in hospital but usually requires approximately 2 to 3 days off work (depending on the nature of your work). ***This procedure requires a general anaesthetic.***

3. Specialist re-assessment and non-surgical management (eg drugs or creams, physiotherapy, or steroid injections)

If you are allocated to this group, you will not receive any surgery. Instead, you will have a specialist re-assessment of your condition with the consultant surgeon responsible for your care. (S)he might recommend a number of treatments eg physiotherapy or injection depending on your symptoms.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any time and this would not affect your current or future medical treatment. The information we already have will be stored securely and confidentially, unless you request that we delete it.

What if something goes wrong?

We do not expect any harm to come to you by taking part in this study. However, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms (which includes professional indemnity insurance) would be available to you.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (KORAL co-ordinating office 01224 554338). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised.

Your name will not be written on any of the follow up questionnaires. The information you give us will be kept secure using passwords. Any information you provide will be seen by the research team only.

Involvement of the General Practitioner/Family doctor (GP)

With your permission, we will inform your GP that you are taking part.

What will happen to the results of the research study?

The results of this pilot study will help us to plan a full scale trial for the UK. It will help us make sure that the design of the trial is acceptable to surgeons and patients.

Who is organising and funding the research?

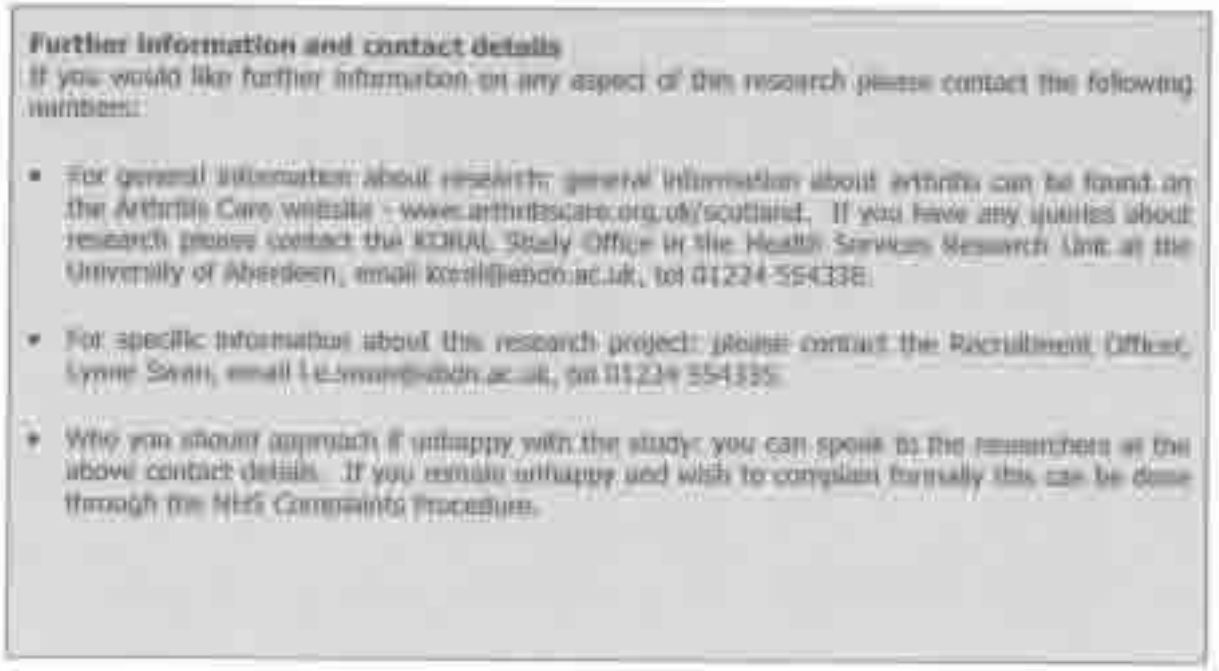
The study is funded by the Department of Health Research and Development Health Technology Assessment Programme. A team based in the University of Aberdeen is responsible for the day-to-day management of the study. However, your hospital is taking part in the study and your doctor is part of the collaborating team.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by North West Research Ethics Committee.

What if relevant new information becomes available?

Sometimes we get new information about the procedure being studied. If this happens, your hospital doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your hospital doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form. If this happens, your hospital doctor might consider you should withdraw from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.



Further information and contact details

If you would like further information on any aspect of this research please contact the following numbers:

- For general information about research: general information about arthritis can be found on the Arthritis Care website - www.arthritiscare.org.uk/scotland. If you have any queries about research please contact the KORAL Study Office in the Health Services Research Unit at the University of Aberdeen, email koral@abdn.ac.uk, tel 01224 554338.
- For specific information about this research project: please contact the Recruitment Officer, Lynne Swan, email l.e.swan@abdn.ac.uk, tel 01224 554335.
- Who you should approach if unhappy with the study: you can speak to the researchers at the above contact details. If you remain unhappy and wish to complain formally this can be done through the NHS Complaints Procedure.

Thank you for reading this

KORAL STUDY OFFICE
Health Services Research Unit
University of Aberdeen
Forresterhill
Aberdeen, AB25 2ZD
Tel: 01224 554338
Fax: 01224 554560
Email: koral@abdn.ac.uk

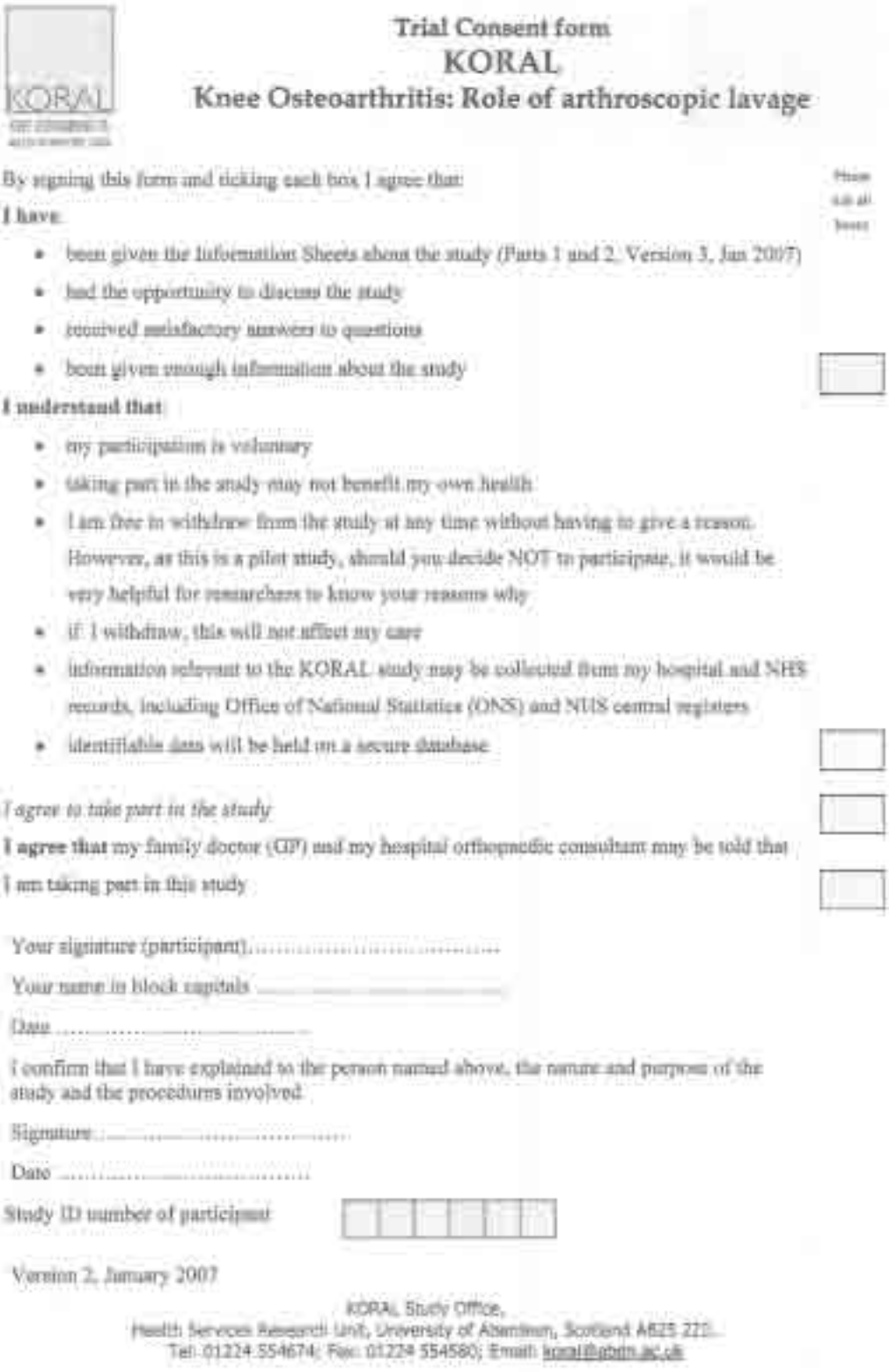
Local details

Clinical lead:

Recruitment Officer:

Appendix 11

Consent form



Trial Consent form
KORAL
Knee Osteoarthritis: Role of arthroscopic lavage

By signing this form and ticking each box I agree that:

I have

- been given the Information Sheets about the study (Parts 1 and 2, Version 3, Jan 2007)
- had the opportunity to discuss the study
- received satisfactory answers to questions
- been given enough information about the study

I understand that

- my participation is voluntary
- taking part in the study may not benefit my own health
- I am free to withdraw from the study at any time without having to give a reason. However, as this is a pilot study, should you decide NOT to participate, it would be very helpful for researchers to know your reasons why
- if I withdraw, this will not affect my care
- information relevant to the KORAL study may be collected from my hospital and NHS records, including Office of National Statistics (ONS) and NUS central registers
- identifiable data will be held on a secure database

I agree to take part in the study

I agree that my family doctor (GP) and my hospital orthopaedic consultant may be told that I am taking part in this study

Your signature (participant).....

Your name in block capitals .....

Date .....

I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved.

Signature .....

Date .....

Study ID number of participant

Version 2, January 2007

KORAL Study Office,
Health Services Research Unit, University of Aberdeen, Scotland AB25 2ZD.
Tel: 01224 554674; Fax: 01224 554580; Email: koral@abdn.ac.uk

Appendix 12

Case report forms and questionnaires

Ineligible or Declined

Outline data on patients who are ineligible or who decline participation

Q1 Date of attempted recruitment DD/MM/YY ☐☐ / ☐☐ / ☐☐

Q2 Gender

☐ Male ☐ Female

Q3 Age

☐☐

Q4 Centre

☐☐

Q5 Reasons for non-inclusion - tick all that apply

Arthroscopic lavage clearly indicated ❑
Arthroplasty clearly indicated ❑
Clear contra-indication to anaesthesia ❑
Patient does not understand English ❑
Patient unable to complete follow-up questionnaires ❑
Patient does not want to participate in the study: ❑
- does not like the idea of the study ❑
- does not like the idea of a placebo ❑
Other ❑

If other, please state:

Signature: _____

STUDY No. | | | | | |

CONFIDENTIAL

KORAL STUDY

ARTHROSCOPIC LAVAGE IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

PARTICIPANT DETAILS FORM

Thank you for helping us with our research

We would be very grateful if you could complete and return this form.

ISRCTN02328576

Version 1 May 2006

PERSONAL INFORMATION

Title *(Mr, Mrs etc)*

Surname

First Names

Date of Birth Day / Month / Year

Gender
Male Female

Maiden name if female and ever married

Address

Postcode

Telephone Number (including code)

Mobile Number

NHS Number

Hospital Number (if known)

CHI Number (Scotland only)

GENERAL PRACTITIONER

Surname

First Name(s) (if known)

Address

Postcode

Telephone Number (including code)

To be completed on withdrawal from the study

Study No

1. Date of withdrawal (dd/mm/yy)

Reason for withdrawal

2. Participant decided to withdraw (state reason)

3. Any medical reasons for withdrawal? (state reason)

4. Continued use of data

Does the participant agree to relevant data being collected in the future through central sources (eg hospital notes)? Yes ☐ No ☐

ISRCTN02328576
Version 1 July 2006

Clinical data sheet

Study No | | | | | |

Date of clinic (DD/MM/YY) | | / | | / | |

1. Study Knee
   - Right ☐
   - Left ☐

2. ASA Grade – fit for surgery?
   - Yes ☐
   - No ☐

3. X-ray grading *(Kellgren-Lawrence)*
   - 0 ☐
   - 1 ☐
   - 2 ☐
   - 3 ☐
   - 4 *(ineligible)* ☐

4. Mechanical Symptoms present?
   - Yes *(and therefore ineligible)* ☐
   - No ☐

5. Range of motion
   - Hyperextension °
   - Flexion °
   - Neutral Yes ☐ No ☐
   - If No, fixed flexion deformity °

6. Effusion
   - 0 none ☐
   - + mild ☐
   - ++ mod ☐
   - +++ severe ☐

7. Limb alignment 1 *(with patient standing)*

   Normal *(medial malleoli and medial femoral condyles touch)* Yes ☐ No ☐

   Varus Yes ☐ No ☐ **If Yes**, gap between medial femoral condules ☐☐ cms

   Valgus Yes ☐ No ☐ **If Yes**, gap between medial malleoli ☐☐ cms

8. Limb alignment 2 — Femoro-tibial angle °

9. Height ☐☐☐ cms

10. Weight ☐☐☐ kgs

ISRCTN02328576
Version 1 July 2007

MEDICAL MANAGEMENT

Date | | | | | | | | Study No | | | | | |

		YES			YES
1.	**Analgesia**		2.	**Support**	
	Simple	☐		Walking stick	☐
	NSAID	☐		Elastic knee brace	☐
	Other	☐		Other	☐
	If other, specify				

3.	**Heat or Ice**	☐	4.	**Lifestyle modification advice**	☐
5.	**Exercise**		6.	**Injection**	
	Referral	☐		Steroid	☐
	Exercise sheet	☐		HA	☐
7.	**Glucosamine**	☐	8.	**Chondroitin**	☐
9.	**Other**	☐		**If other, specify**	

Version 1, July 2005

MEDICAL MANAGEMENT FOLLOW-UP CLINIC

Study No | | | | | |

Date of clinic (DD/MM/YY) | | / | | / | |

1. Study Knee

Right ☐

Left ☐

2. Range of motion

Hyperextension ☐ ° Neutral Yes ☐ No ☐

Flexion ☐ ° If No, fixed flexion deformity ☐ °

3. Effusion

0 none ☐ ++ mod ☐

+ mild ☐ +++ severe ☐

4. Weight kgs ☐

5. Any other treatment/surgery planned?

Yes ☐

No ☐

6a. **If yes**, what? ☐

6b. **If yes**, when? ☐

7. Any clinical follow-up planned?

Yes ☐

No ☐

7a. **If yes**, what? ☐

7b. **If yes**, when? ☐

8. Any change of symptoms? ☐

RANDOMISED TO SURGERY - PARTICIPANT DETAILS

Date of clinic | | | / | | | / | | |

1. Study number | | | | | | |
2. Hospital number | | | | | | | | | | | |
3. Surname | |
4. First Name(s) | |
5. Address | |
| |
| |
6. Surgery code | | | | |

ISRCTN02328576
Version 1 July 2007

Anaesthetic details

Study No

1 Grade of anaesthetist

- Consultant ☐
- Associate Specialist/Staff Grade ☐
- Specialist Trainee ☐

2 Patient's ASA grade

- I ☐
- II ☐
- III or above *(ineligible)* ☐

3 Induction agent

- Propofol ☐
- Thiopentone ☐
- Other ☐

4 OPIOID

- Short acting (Fentanyl/Alfentanil) ☐
- Long Acting (Morphine) ☐

5 Maintenance

- Nitrous Oxide ☐
- Volatile ☐
- Volatile ☐

6 Analgesia (post-op)

- NSAID ☐
- Paracetamol ☐
- OPIOID ☐

7 Airway

- MASK ☐
- LMA ☐
- Tracheal Tube ☐

8 Time into Anaesthetic Room *(hh:mm)* ☐☐ : ☐☐

9 Time into Theatre ☐☐ : ☐☐

10 Time into Recovery ☐☐ : ☐☐

ISRCTN02328576
Version 1 July 2007

Surgical details

If randomised to arthroscopic lavage, complete all pages. If randomised to placebo operation, complete pages 1 and 2 only.

Study No

Date of surgery (DD/MM/YY) ☐☐ / ☐☐ / ☐☐

Randomised to: Arthroscopy ☐ Placebo operation ☐

Tourniquet **Yes** ☐ **No** ☐ If Yes Mins ☐ mmHg ☐

EUA:

Hyperextension ☐ ° **Extension deficit** ☐ ° **Flexion** ☐ °

Effusion	0 none	☐	**Lachman**	0-2mm	☐	**Pivot**	0 none	☐
	+ mild	☐		3-5mm	☐	**Shift**	+ glide	☐
	++ mod	☐		6-9mm	☐		++clunk	☐
	+++ severe	☐		≥10mm	☐		+++ gross	☐
				Firm	☐			
				Not Firm	☐			
MCL	0-2mm	☐	**LCL**	0-2mm	☐	**PCL**	0-2mm	☐
	3-5mm	☐		3-5mm	☐		3-5mm	☐
	6-9mm	☐		6-9mm	☐		6-9mm	☐
	≥10mm	☐		≥10mm	☐		≥10mm	☐

Other

Grade of surgeon: **Confirm Consultant *(as per protocol)*** ☐

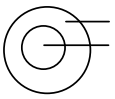
Date of hospital discharge (DD/MM/YY) ☐☐ / ☐☐ / ☐☐

LA	20ml 0.5% Marcain		
Dressing	Steristrips ☐ Suture☐		opsite, gauze, wool, crepe
Post-Op	Routine care, mobilise ASAP. Reduce dressing to DTG at discharge		
Follow-up		**Physio**	
Other			
Signed			

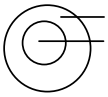
Modified Noyes Rating

Lesion Score		**10mm**	**15mm**
1 Chondromalacia:	A soft,	1	2
	B softening, indentation	1	2
2 Open Lesion thickness	A Fissure/fragmentation half	2	3
	B Fissure/fragmentation full thickness	3	6
3 Bone	A exposed,	5	10
	B bone cavity	5	10

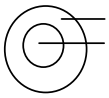
Complex lesions - Examples



1B (Chondromalacia, 15mm dia)
2A (Fissures, 10mm dia)
3 points



2A (Fissures, 15mm dia)
2B (Fissures, 10mm dia)
4 points



2B (Fissures, 15mm dia)
3A (Bone, 10mm dia)
7 points

Anatomical Score **Score**

Patella ☐ + **Femoral sulcus** ☐ = ☐

Medial Femur ☐ + **Medial Tibia** ☐ = ☐

Lateral Femur ☐ + **Lateral Tibia** ☐ = ☐

Total score ☐

Was debridement done? Yes ☐ No ☐

If yes, please indicate type of debridement:

Miniscus ☐

Articular cartilage ☐

Other *(please describe)* ☐ ☐

Subjective findings

ARTHROSCOPY **Incisions : Medial, lateral, lateral suprapatellar**
Findings and Action

Patello-femoral	
Gutters	
Medial	
Lateral	
Medial Meniscus	
Lateral Meniscus	
ACL/PCL/Notch	

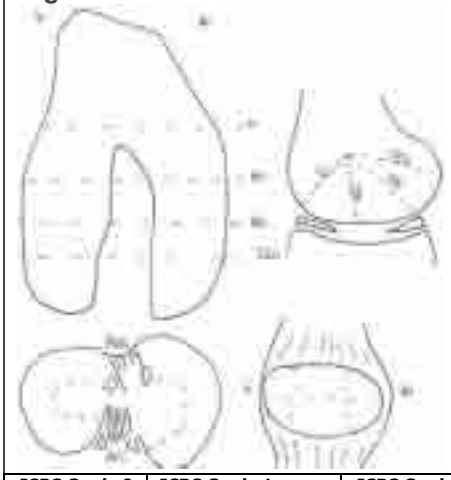
Right Menisci

Left Menisci

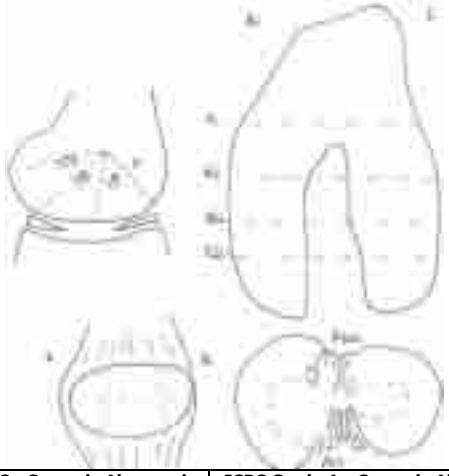
ICRS rating

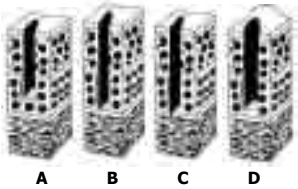
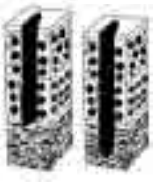
Draw chondral lesions on appropriate diagram, then record lesion grade and size

Right Knee Joint Surfaces



Left Knee Joint Surfaces



ICRS Grade 0 – Normal	**ICRS Grade 1 – Nearly Normal Superficial lesions, Soft indentation (A) and/or superficial fissures and cracks (B)**	***ICRS Grade 2 – Abnormal***	**ICRS Grade 3 - Severely Abnormal**	***ICRS Grade 4 – Severely Abnormal***
		Lesions extending down to <50% of cartilage depth	Cartilage defects extending down >50% of cartilage depth (A) as well as down to calcified layer (B) and down to Blisters are included in this Grade (D)	Osteochondral injuries, lesions extending just through the subchondral boneplate (A) or deeper defects down into trabecular bone (B). Defects that have been drilled are regarded as osteochondral defects and classified as ICRS-C
	 A B		 A B C D	 A B

Surgical follow-up clinic

Study No | | | | | |

Date of clinic (DD/MM/YY) | | | / | | | / | | |

1. Study Knee

   Left ☐ Right ☐

2. Wound healed?

   Yes ☐

   No ☐ If no, please give details

3. Any evidence of inflammation?

   No ☐

   Yes ☐ If yes, please give details

4. Have there been problems since surgery over and above normal post-operative issues (eg infection treated by antibiotics, persistent discharge)?

   No ☐

   Yes ☐ If yes, please give details

5. Was the patient re-admitted to hospital?

   No ☐

   Yes ☐ If yes, please give details

6. Was the patient discharged on the day of surgery?

   Yes ☐

   No ☐ If no, please give details

7. Range of motion

Hyperextension	°	Extension deficit (0 if neutral)	°	Flexion	°

8. Effusion

0 none	☐	++ mod	☐
+ mild	☐	+++ severe	☐

9. Any other treatment/surgery planned?

Yes ☐
No ☐

9a. **If yes**, what?

9b. **If yes**, when?

10. Any **clinical follow-up** planned?

Yes ☐
No ☐

10a. **If yes**, what?

10b. **If yes**, when?

There will be additional patient follow-up (by postal questionnaire) – these questionnaires will be administered by the KORAL team.

Serious Adverse Event Report

To be completed for any serious adverse events

Study No

1. **Date of report (dd/mm/yy)**

2. **Name of person initially reporting adverse event**

Contact details **Address**

Telephone

Email

PATIENT DETAILS

3. **Patient's Initials**

4. **Date of birth**

5. **Hospital number**

6. **Sex**

Male Female

7. **Place where adverse event took place/detected**

8. **Date of event**

9 Brief details of adverse event

10. Cross all appropriate to adverse event – if any boxes are crossed the adverse event is "serious".

Patient died	❑
Involved or prolonged inpatient hospitalisation	❑
Involved persistent or significant disability or incapacity	❑
Life threatening	❑

11. Is this serious adverse event one of XXXXXXX (eg post-operative infection) and therefore an "expected" serious adverse event?

Yes	❑
No	❑

12. Other relevant history (e.g. diagnostics, allergies, etc)

Assessment of whether event was caused by trial participation

13. Is it reasonably likely that the adverse event was caused by taking part in KORAL

Yes	❑
No	❑

14. Why

15. Name and position of person making this judgment

16. Any subsequent information

STUDY No. | | | | | |

CONFIDENTIAL

KORAL STUDY

ARTHROSCOPIC LAVAGE FOR TREATMENT OF OSTEOARTHRITIS OF THE KNEE

BASELINE QUESTIONNAIRE

Thank you for helping us with research into osteoarthritis of the knee. We would be very grateful if you could complete and return this questionnaire.

ISRCTN02328576
Version 1 May 2006

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

The following questions ask about problems which may have been caused by your knee during **the past 4 weeks**.

A1. During the past 4 weeks how would you describe the pain you have from your knee?

(*Cross **ONE** box only*)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐

A2. During the past 4 weeks have you had any trouble with washing and drying yourself (all over) because of your knee?

(*Cross **ONE** box only*)

- No trouble at all ☐
- Very little trouble ☐
- Moderate trouble ☐
- Extreme trouble ☐
- Impossible to do ☐

A3. During the past 4 weeks have you had any trouble getting in and out of a car or using public transport because of your knee? (whichever you tend to use).

(*Cross **ONE** box only*)

- No trouble at all ☐
- Very little trouble ☐
- Moderate trouble ☐
- Extreme difficulty ☐
- Impossible to do ☐

A4. During the past 4 weeks for how long have you been able to walk before the pain from your knee becomes severe? (with or without a stick).

(*Cross **ONE** box only*)

- No pain at all, or no pain for more than 30 mins ☐
- 16 to 30 mins ☐
- 5 to 15 mins ☐
- Around the house only ☐
- Not at all - severe on walking ☐

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

A5. During the past 4 weeks after a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

(*Cross **ONE** box only*)

- ☐ Not at all painful
- ☐ Slightly painful
- ☐ Moderately painful
- ☐ Very painful
- ☐ Unbearable

A6. During the past 4 weeks have you been limping when walking, because of your knee?

(*Cross **ONE** box only*)

- ☐ Rarely/never
- ☐ Sometimes or just at first
- ☐ Often, not just at first
- ☐ Most of the time
- ☐ All of the time

A7. During the past 4 weeks could you kneel down and get up again afterwards? (thinking of your knee)

(*Cross **ONE** box only*)

- ☐ Yes, easily
- ☐ With little difficulty
- ☐ With moderate difficulty
- ☐ With extreme difficulty
- ☐ No, impossible

A8. During the past 4 weeks have you been troubled by pain from your knee in bed at night?

(*Cross **ONE** box only*)

- ☐ No, never
- ☐ Only 1 or 2 nights
- ☐ Some nights
- ☐ Most nights
- ☐ Every night

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

A9. During the <u>past 4 weeks</u> how much has pain from your knee interfered with your usual work (including housework)?

(*Cross **ONE** box only*)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Greatly ☐
- Totally ☐

A10. During the <u>past 4 weeks</u> have you felt that your knee might suddenly "give way" or let you down?

(*Cross **ONE** box only*)

- Rarely/never ☐
- Sometimes or just at first ☐
- Often, not just at first ☐
- Most of the time ☐
- All of the time ☐

A11. During the <u>past 4 weeks</u> could you do the household shopping on your own? (thinking of your knee)

(*Cross **ONE** box only*)

- Yes, easily ☐
- With little difficulty ☐
- With moderate difficulty ☐
- With extreme difficulty ☐
- No, impossible ☐

A12. During the <u>past 4 weeks</u> could you walk down a flight of stairs? (thinking of your knee)

(*Cross **ONE** box only*)

- Yes, easily ☐
- With little difficulty ☐
- With moderate difficulty ☐
- With extreme difficulty ☐
- No, impossible ☐

SECTION B – DESCRIBING YOUR OWN HEALTH TODAY

The next two sections are about your general health.

By placing a cross (X) in one box in each group below, please indicate which statement best describes your own health state today. Do not X more than one box in each group.

B1. Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

B2. Self-Care

I have no problems with self care	☐
I have some problems washing and dressing myself	☐
I am unable to wash myself	☐

B3. Usual activities (eg work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

B4. Pain / Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

B5. Anxiety / Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today.

Your own health state today

SECTION C – GENERAL HEALTH SF12 ©

The following questions ask for your views about your health **in the last 4 weeks,** how you feel and how well you are able to do your usual activities.

Answer every question by placing a cross in one box only. If you are unsure about how to answer any questions please give the best answer you can.

C1. In general, would you say your health is:

(*Cross **ONE** box only*)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

C2. During a typical day does your health limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf? If so, how much?

(*Cross **ONE** box only*)

- Yes, limited a lot ☐
- Yes, limited a little ☐
- No, not limited at all ☐

C3. During a typical day does your health limit you in climbing several flights of stairs? If so, how much?

(*Cross **ONE** box only*)

- Yes, limited a lot ☐
- Yes, limited a little ☐
- No, not limited at all ☐

SECTION C – GENERAL HEALTH SF12 ©

C4. During the <u>past 4 weeks</u>, how often have you accomplished less than you would have liked in your work or other regular daily activities as a result of your physical health?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C5. During the <u>past 4 weeks</u>, how often have you been limited in performing any kind of work or other regular daily activities as a result of your physical health?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C6. During the <u>past 4 weeks</u>, how often have you accomplished less than you would have liked in your work or any other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION C – GENERAL HEALTH SF12 ©

C7. During the past 4 weeks, how often have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C8. During the past 4 weeks how much did pain interfere with your normal work (both outside the home and housework)?

*(Cross **ONE** box only)*

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

C9. How much during the past 4 weeks have you felt calm and peaceful?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION C – GENERAL HEALTH SF12 ©

C10. How much during the past 4 weeks did you have a lot of energy?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C11. How much during the past 4 weeks have you felt downhearted and depressed?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C12. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION D – PAIN

Please indicate on this scale how you would rate your pain today? The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a cross (X) on the line that best indicates the rating of your pain today.

Thank you for filling in this questionnaire, please post it back to us in the envelope provided

If you would like any further information or have any queries about the study, please contact:

The KORAL Study Office in Aberdeen (Tel: 01224 554338)

This study is taking place in centres across the UK but the questionnaires are being processed in Aberdeen at the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, 3rd Floor, Health Sciences Building, Foresterhill, ABERDEEN, AB25 2ZD.

KORAL
KNEE OSTEOARTHRITIS:
ROLE OF ARTHROSCOPIC LAVAGE

STUDY No | | | | | |

CONFIDENTIAL

KORAL STUDY

ARTHROSCOPIC LAVAGE FOR TREATMENT OF OSTEOARTHRITIS OF THE KNEE

FOLLOW UP QUESTIONNAIRE

Thank you for helping us with research into osteoarthritis of the knee. We would be very grateful if you could complete and return this questionnaire.

ISRCTN02328576
Version 2, December 2007

2MPQ

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

The following questions ask about problems which may have been caused by your knee during the **past 4 weeks**.

A1. During the past 4 weeks how would you describe the pain you have from your knee?

(*Cross **ONE** box only*)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐

A2. During the past 4 weeks have you had any trouble with washing and drying yourself (all over) because of your knee?

(*Cross **ONE** box only*)

- No trouble at all ☐
- Very little trouble ☐
- Moderate trouble ☐
- Extreme trouble ☐
- Impossible to do ☐

A3. During the past 4 weeks have you had any trouble getting in and out of a car or using public transport because of your knee? (whichever you tend to use).

(*Cross **ONE** box only*)

- No trouble at all ☐
- Very little trouble ☐
- Moderate trouble ☐
- Extreme difficulty ☐
- Impossible to do ☐

A4. During the past 4 weeks for how long have you been able to walk before the pain from your knee becomes severe? (with or without a stick).

(*Cross **ONE** box only*)

- No pain at all, or no pain for more than 30 mins ☐
- 16 to 30 mins ☐
- 5 to 15 mins ☐
- Around the house only ☐
- Not at all - severe on walking ☐

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

A5. During the <u>past 4 weeks</u> after a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

(*Cross **ONE** box only*)

- Not at all painful ☐
- Slightly painful ☐
- Moderately painful ☐
- Very painful ☐
- Unbearable ☐

A6. During the <u>past 4 weeks</u> have you been limping when walking, because of your knee?

(*Cross **ONE** box only*)

- Rarely/never ☐
- Sometimes or just at first ☐
- Often, not just at first ☐
- Most of the time ☐
- All of the time ☐

A7. During the <u>past 4 weeks</u> could you kneel down and get up again afterwards? (thinking of your knee)

(*Cross **ONE** box only*)

- Yes, easily ☐
- With little difficulty ☐
- With moderate difficulty ☐
- With extreme difficulty ☐
- No, impossible ☐

A8. During the <u>past 4 weeks</u> have you been troubled by pain from your knee in bed at night?

(*Cross **ONE** box only*)

- No, never ☐
- Only 1 or 2 nights ☐
- Some nights ☐
- Most nights ☐
- Every night ☐

SECTION A - HEALTH PROBLEMS CAUSED BY YOUR KNEE

A9. During the <u>past 4 weeks</u> how much has pain from your knee interfered with your usual work (including housework)?

(*Cross **ONE** box only*)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Greatly ☐
- Totally ☐

A10. During the <u>past 4 weeks</u> have you felt that your knee might suddenly "give way" or let you down?

(*Cross **ONE** box only*)

- Rarely/never ☐
- Sometimes or just at first ☐
- Often, not just at first ☐
- Most of the time ☐
- All of the time ☐

A11. During the <u>past 4 weeks</u> could you do the household shopping on your own? (thinking of your knee)

(*Cross **ONE** box only*)

- Yes, easily ☐
- With little difficulty ☐
- With moderate difficulty ☐
- With extreme difficulty ☐
- No, impossible ☐

A12. During the <u>past 4 weeks</u> could you walk down a flight of stairs? (thinking of your knee)

(*Cross **ONE** box only*)

- Yes, easily ☐
- With little difficulty ☐
- With moderate difficulty ☐
- With extreme difficulty ☐
- No, impossible ☐

SECTION B – DESCRIBING YOUR OWN HEALTH TODAY

The next two sections are about your general health.

By placing a cross (X) in one box in each group below, please indicate which statement best describes your own health state today. Do not X more than one box in each group.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self care	☐
I have some problems washing and dressing myself	☐
I am unable to wash myself	☐

Usual activities (eg work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain / Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety / Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today.

Your own health state today

SECTION C – GENERAL HEALTH SF12 ©

The following questions ask for your views about your health **in the last 4 weeks**, how you feel and how well you are able to do your usual activities.

Answer every question by placing a cross in one box only. If you are unsure about how to answer any questions please give the best answer you can.

C1. In general, would you say your health is:

(*Cross **ONE** box only*)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

C2. During a typical day does your health limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf? If so, how much?

(*Cross **ONE** box only*)

- Yes, limited a lot ☐
- Yes, limited a little ☐
- No, not limited at all ☐

C3. During a typical day does your health limit you in climbing several flights of stairs? If so, how much?

(*Cross **ONE** box only*)

- Yes, limited a lot ☐
- Yes, limited a little ☐
- No, not limited at all ☐

SECTION C – GENERAL HEALTH SF12 ©

C4. During the <u>past 4 weeks</u>, how often have you accomplished less than you would have liked in your work or other regular daily activities as a result of your physical health?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C5. During the <u>past 4 weeks</u>, how often have you been limited in performing any kind of work or other regular daily activities as a result of your physical health?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C6. During the <u>past 4 weeks</u>, how often have you accomplished less than you would have liked in your work or any other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION C – GENERAL HEALTH SF12 ©

C7. During the <u>past 4 weeks</u>, how often have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C8. During the <u>past 4 weeks</u> how much did pain interfere with your normal work (both outside the home and housework)?

*(Cross **ONE** box only)*

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

C9. How much during the <u>past 4 weeks</u> have you felt calm and peaceful?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION C – GENERAL HEALTH SF12 ©

C10. How much during the past 4 weeks did you have a lot of energy?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

C11. How much during the past 4 weeks have you felt downhearted and depressed?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

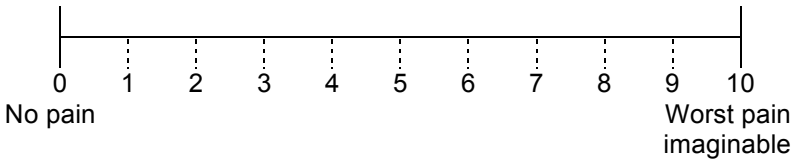
C12. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

*(Cross **ONE** box only)*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

SECTION D – PAIN

D1. Please indicate on this scale how you would rate your <u>pain</u> today? The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a cross (X) on the line that best indicates the rating of your pain <u>today</u>.



D2. If you are currently being PRESCRIBED any medication to manage your pain, please list below the name(s) of the medicine(s) and include the number of times you have taken it in the last two weeks.

Name of medication	No. of times taken in the last 2 weeks

D3. Please list below the names of any NON PRESCRIBED (over the counter) medication you take for your pain and include the number of times you have taken it in the last two weeks.

Name of medication	No. of times taken in the last 2 weeks

SECTION E – YOUR FOLLOW-UP

E1. In the study you were randomised to surgery or to non-surgical management. People who were randomised to surgery either had surgery (arthroscopic lavage) or placebo surgery (a simulated arthroscopic lavage that mimics the surgical procedure).

If you had surgery on your knee as part of the KORAL study, which type of surgery do you think you had?

Surgery (arthroscopic lavage) ☐

Placebo surgery (simulated arthroscopic lavage) ☐

*(Cross **ONE** box only)* Don't know ☐

Thank you for filling in this questionnaire, please post it back to us in the envelope provided

If you would like any further information or have any queries about the study, please contact:

The KORAL Study Office in Aberdeen (Tel: 01224 554338)

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Effectiveness and cost-effectiveness of arthroscopic lavage in the treatment of osteoarthritis of the knee: a mixed methods study of the feasibility of conducting a surgical placebo-controlled trial (the KORAL study)

MK Campbell, ZC Skea, AG Sutherland, BH Cuthbertson, VA Entwistle, AM McDonald, JD Norrie, RV Carlson, S Bridgman and the KORAL study group

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