Protocol HTA 17/138

1. HTA 17/138

2. The clinical effectiveness and cost effectiveness of Surgery for early osteoarthritis of the hip and knee joint

3. Background and Rationale

Describing the condition

Worldwide musculoskeletal disorders accounted for 6-8% of all disability-adjusted life years (DALYS) and osteoarthritis accounts for approximately 10% of this disease burden[1]. In the UK, more people receive disability living allowance as a result of arthritis than received for heart disease, stroke, chest disease and cancer combined (Department of Work and Pensions).

Osteoarthritis (OA) affecting the knee is common with a global prevalence of radiographically confirmed symptomatic knee OA estimated to be 3.8%[2] and a lifetime risk of symptomatic knee OA in western populations estimated to be over 40%[3]. Knee OA can affect all three compartments of the knee in isolation or present in a multi-compartmental pattern.

Osteoarthritis of the hip may also develop during early adulthood, usually due to adverse biomechanics arising from the developmental conditions hip dysplasia or femoroacetabular impingement[4]. Hip dysplasia describes a shallow acetabulum[5], whereas femoroacetabular impingement results from subtle shape abnormalities of the femoral head or acetabulum[6]. These conditions lead to abnormal pressures upon the joint cartilage that can progress to osteoarthritis.

OA disease is a joint wide condition characterised by damage to the articular surfaces of the joint, bone sclerosis and cysts, stiffness of the soft-tissues around the knee, synovitis and intermittent joint effusions. These features may be described as structural osteoarthritis. In addition to these findings, patients may or may not describe a broad set of symptoms, characterised by pain and stiffness in the joint that produces a reduction in function and ultimately in quality of life. These individuals have clinical osteoarthritis. Genetic, acquired and environmental factors all play a role in the pathogenesis of the hip and knee osteoarthritis[7]. In most cases the natural history of the disease process is usually long and protracted, occurring over decades.

Many patients with structural hip and knee OA have no or very mild symptoms from their joint. However, there is a group of patients with early or late OA structural changes who develop more pronounced hip or knee pain and loss of function, described as clinical osteoarthritis[8,9]. All patients who present with clinical OA should undergo initial treatment following the NICE clinical guidelines for treatment, with good information, physical therapy and weight loss if appropriate. Second line measures can be introduced to treatment such as knee injection[10].

For patients with severe symptoms and end-stage structural hip or knee OA, non-operative measures do not always control symptoms sufficiently, and patients are referred to secondary care to discuss joint replacement (arthroplasty) as a possible treatment option[10]. The average of age of these patients is in their mid to late 60s and joint replacement is successful for the majority of patients[11-13].

Patients with early OA of the knee or hip can also have marked symptoms that do not settle with non-operative treatment and continue to cause disability[11]. We have previously

shown that early knee OA patients can present with symptom levels as severe as those with end-stage disease who are considering joint replacement[8]. These patients are typically a younger group of patients and are said to have entered the 'treatment gap', where symptoms and disability can be significant and yet treatment options are limited[14].

Arthroplasty is a very effective treatment for pain but involves a major operation with a risk of complications. In young patients surgeons are reluctant to offer operations that will need to be revised in the future, typically after 10-15 years, which is a complex operation with greater morbidity. The results are less reliable when structural knee OA is less severe, even if pain is severe. There is uncertainty about whether arthroplasty should be used in moderate OA or at younger ages, leading many patients to persist with pain and disability without an effective treatment.

For many years arthroscopic lavage or 'wash-out' of the knee joint was considered a first line treatment in the early OA group. However joint wash-out[15], together with meniscectomy[16], has been shown to be ineffective if indiscriminately used in the OA patient and the practice has greatly reduced[17]. Other arthroscopic procedures have become more widely used such as chondroplasty in the knee[18] and osteochondral surgery for femoroacetabular impingement in the hip[19]. There are many other procedures in clinical use but with variable uptake around the country. Osteotomies (realignment of the bones around the joint) can be used in the knee or hip, with controversy about their ideal indication and benefit over a strategy of early arthroplasty. Also, multiple procedures have been developed to stimulate new cartilage growth in the joint, or prevent further deterioration (such as chondroplasty, microfracture, autologous chondrocyte implantation, or joint distraction). However for many procedures there appears to be more limited evidence, with variable descriptions of their use in early and moderate OA and subsequently no treatment guidelines for their use in this population. This has lead to variations in commissioning and surgeon uptake, with uncertainty about the best approach to this common problem.

Definition of early osteoarthritis (EOA) of the knee and hip

We are in the process of completing a Cochrane review on the use of surgery in early knee OA, which has helped formulate this application[20]. We have spent considerable time defining 'early osteoarthritis' and have extended this thinking to the early hip OA population. OA is a joint wide process but in terms of stratifying OA disease to guide treatment pathways the state of the articular cartilage within the joint is central to choosing surgical treatment. Therefore we have used a broad definition with focus on the presence of pain and the exclusion of people with diffuse full-thickness disease who would normally be considered suitable for arthroplasty surgery. This follows the clinical treatment of OA patients where the majority of joint replacements are performed for clinical end-stage OA of the hip or knee, with extensive failure of joint structures such as major cartilage loss, bony eburnation and in some cases bone loss. Early clinical hip or knee OA (EHKOA) represents the presence of symptoms, and more focused structural change usually starting in one geographically distinct region of the joint. In addition within the joint structural articular cartilage damage may be seen in combination with other morphological features that predispose to early joint failure, such as In dysplasia[5] and femoroacetabular impingement (FAI)[6] in the hip and metaphyseal varus in the knee[21,22].

This definition of early osteoarthritis reflects the currently used indications for surgical treatment. There are a very broad range of patients with reproducible patterns of disease both in hip and knee, where articular cartilage damage may be very minor through to focal full thickness cartilage loss, together with other joint changes This cohort does not include individuals with end-stage OA joint failure where there is widespread cartilage loss and potentially eburnated bone or bone loss. The definitions of early structural hip and knee OA used in this study are seen in Table 1 and are provided in more detail in the Methods section below.

Hip: Early structural OA
(1) KL Grade 1-3 of weight-bearing AP radiograph
(2) Partial thickness cartilage loss or delamination on MRI.
(3) Focal full-thickness cartilage loss in the hip on MRI
(4) Cartilage changes affecting the joint seen at arthroscopy or open surgery
Knee: Early structural OA
(1) KLGrade 1-3 of weight-bearing AP radiograph
(2) Partial thickness cartilage loss on MRI.
(3) Focal full-thickness loss in one compartment of the knee on MRI greater th $2cm^2$
(4) Cartilage changes affecting the joint seen at arthroscopy or open surgery

(KL = Kellgren-Lawrence grading system[23])

Table 1 Outline definitions of early structural OA of the hip and knee. - a broad spectrum of joint changes that occur before 'end-stage OA'

Surgical treatment for early hip and knee OA

In present practice surgical procedures for osteoarthritis of the hip or knee are only indicated in patients who have clinical osteoarthritis where both symptoms and structural OA change are present. This is most obviously seen in end-stage disease where the aim of joint replacement is to reduce symptoms. The same indications are used in current surgical practice to treat early hip or knee OA. However, the aims of the intervention are two-fold; symptom relief and slowing structural progression to end-stage disease and potentially avoiding joint replacement surgery.

Our understanding of the range of procedures that are performed to treat early clinical hip and knee osteoarthritis is based on our Cochrane Review entitled Surgical interventions for early knee OA[20] (Review number: A113-R – in final stages of editing process), very recent scoping reviews (including RCT and cohort studies) of surgical procedures for treating early hip and knee OA performed in the preparation of this grant proposal and the supporting evidence and guidance provided within the HTA call.

As outlined in the HTA call there are two major surgical treatment types; joint preservation and joint replacement. Further to this our preliminary work has identified four groups of intervention which encompass all current procedures:

Joint preservation - Non-regenerative procedures

In these procedures the goal is to remove or repair pathological tissue within the joint, without aiming to regenerate new tissue. These procedures are aimed at reducing symptoms and reducing risk of progression.

In the knee (arthroscopic or open)
Procedures for early knee osteoarthritis involve trimming (debriding) loose or damaged articular cartilage (chondroplasty) to smooth the surface using punches, shavers, or radiofrequency ablation[18]. The meniscus may also be damaged, and this is addressed by debriding the torn edges or in select cases, performing a meniscal repair (meniscal surgery)[24]. These procedures are performed arthroscopically is a minimally invasive procedure that is offered to patients with early osteoarthritis. Small incisions are made around the joint enabling

the passage of a fibre-optic camera through one incision and surgical instruments through the other portal.

In the hip: (arthroscopic or open)
As with the knee, procedures for early hip osteoarthritis include debriding damaged articular cartilage, and either debriding or repairing damaged labrum. Principal causes of early hip osteoarthritis are dysplasia and femoroacetabular impingement (FAI). FAI describes subtle shape abnormalities of the hip where the femoral head is aspherical (cam morphology) or the acetabulum is deep (pincer morphology). The result is abnormal contact between the ball and socket, leading to joint damage. Osteochondroplasty can be performed to reshape the hip and correct cam or pincer morphology at the same time as cartilage and labral procedures[25]. Where FAI has caused the articular cartilage to detach from the underlying bone, this can be secured back in position using fibrin glue. Osteochondroplasty can be performed with open surgery, but the vast majority of procedures are performed arthroscopically due to shorter recovery times and fewer complications[26].

In this application, the term 'osteochondroplasty' is used to describe arthroscopic procedures of the knee or hip where bone or cartilage is debrided, or meniscus/labrum is debrided or repaired.

Joint preservation - Biological reconstruction of the joint:

Within surgical treatment of early hip and knee arthritis a number of techniques are used within both joints with the aim of replacing biological tissue within the joint. These principally consist of i) subchondral bone marrow stimulation ii) autologous cartilage reconstruction iii) allografts of bone, cartilage or meniscus/labrum, and iv) application of stem cells.

In the hip and knee all the following procedures can be adopted.

Sub-chondral bone marrow stimulation encompasses a variety of techniques. The most widely adopted is microfracture, where the subchondral bone is perforated within a cartilage deficient region to release bone marrow and promote the formation of substitute hyaline cartilage (fibrocartilage). This may be supplemented by a synthetic matrix (autologous matrix-induced chondrogenesis, AMIC)[27].

Autologous chondrocyte implantation (ACI), now mainly third generation matrix-applied chondrocyte implantation (MACI), involves the application of cultured chondrocytes (cartilage producing cells) to regenerate cartilage in areas where it is deficient. Whilst this was appraised recently by NICE[28], the scope limited the assessment to licensed products that have now been overtaken by other technologies on the market, and other technologies are emerging in the literature. It was also focused on isolated chondral lesions rather than osteoarthritis, a wider topic[28,29]. Ongoing uncertainty remains about the cost-effectiveness of ACI in early OA and the criteria for determining if OA is too advanced for the procedure to work[28].

Meniscal/labral and osteochondral allografts can be employed. Meniscal allografts in the fully or functionally menisectomised patient are thought to reduce later OA and improve symptoms[30]. Studies also report reconstruction of the hip labrum using allograft[31]. Osteochondral allografts replace both chondral cartilage and the underlying subchondral bone, which is often abnormal. Their use is increasing in the UK due to emerging long-term follow up data and observational studies, largely from early adopters in the USA[32].

Stem cells (usually harvested from liposuction or bone marrow) have been used in a few studies but have yet to be properly appraised[33]. They were not included in the NICE appraisal of ACI.

Joint preservation - Load modifying procedures;

Osteoarthritis is frequently associated with adverse joint loading, in particular coronal malalignment of the knee and dysplasia of the hip. Load modifying procedures in both joints are used to optimise biomechanics of reducing symptoms and potentially delaying progression.

In the Knee:
An osteotomy for osteoarthritis of the knee joint is a re-alignment procedure aimed at transferring the weight-bearing region of the knee joint from the diseased region to a disease-free region. This is achieved by cutting and re-shaping the bone in the proximal tibia (High tibial osteotomy, HTO) or distal femur (distal femoral osteotomy, DFO). Chronic medial compartment joint-loading can be modified using an extracapsular device. Devices such as the Kinespring® (Moximed, Inc, Hayward, CA, USA) have been developed to partially absorb the load passing through the medial compartment without compromising the joint surface[34]. Metallic interpositional devices are designed to restore medial joint space narrowing caused by osteoarthritis. In so doing a varus knee can be placed into a more neutral alignment[35]. They can be inserted using minimally invasive techniques and have the advantage of being inserted without the need for resection of underlying bone.

In the Hip:
Dysplasia describes a shallow hip acetabulum. It is a potent cause of early hip osteoarthritis due to the resultant small contact area for load transmission between the femur and acetabulum. Periacetabular osteotomies can be performed to reorientate the acetabulum and create a larger contact area for load transmission[36]. When a peri-acetabular osteotomy is not indicated, an alternative is to rotate bone from above the socket to increase the depth of the acetabulum (shelf acetabuloplasty)[37]. Some patients develop hip pathology secondary to abnormal rotation or alignment of the femur that can also be corrected with osteotomies. Osteotomies of the pelvis or femur represent major surgery with a prolonged period of reduced mobility post-operatively.

Joint replacement procedures

Total hip or knee replacement (THR or TKR) involves replacing the surfaces of the knee joint with artificial implants. Unicompartmental knee replacement (UKR) only involves replacing the surfaces of a single diseased compartment (Medial, lateral or patellofemoral) rather than the whole joint surface.

Resurfacing of the hip involves placing a new metal surface over the head of the hip and not implanting a stemmed component. A HTA report on metal on metal hip replacements also covered re-surfacing, based on evidence published before the end of 2012. This underpinned NICE TA guidance 304 issued February 2014.

A small sub-set of metal ‘patch’ replacements have been used in some centres in the knee and these are a distinct group from other types of joint replacement, as they are used to cover a small cartilage defect. There are a small number of papers on this evolving technique which could be included in this review.

Arthroplasty surgery is not routinely offered to those with early hip or knee OA (EKOA) because there is some evidence that it is associated with a poorer outcome, where end-stage bone on bone changes are not present[38,39]. Arthroplasty prostheses may need to be replaced after 10-15 years, and the revision procedure is more difficult with more post-op morbidity, so surgeons are reluctant to carry out TKR or THR in people under 50. Many patients develop early OA much earlier than this, for example because of knee injuries or hip dysplasia.

There is a need to define the optimal pathway for patients with moderate OA or who are young, as arthroplasty may still be preferable to ongoing and prolonged disability, where other treatment options have either failed or are not available. This can be a complicated decision with long-term implications which requires long-term modelling informed by a high-quality literature review.

Why this research is needed now
Indicate the necessity for the research, both in terms of time and relevance.

This research is a commissioned prioritised research call from HTA. In 2015 our group recognised the requirement for a more evidence-based approach to treatment in this area. A significant number of patients have early OA and severe unremitting symptoms but find themselves in the 'treatment gap'. It is not clear whether the surgical procedures offered for this group of patients aimed at reducing symptoms or stopping progression of arthritis are clinically or cost effective. To ensure research priorities were matched with patient and wider-stake holders views, the HTA programme commissioned the James Lind Alliance Priority Setting partnership to identify priorities for research on early hip and knee osteoarthritis.
The Commissioning brief for this project specifies "Patients with early osteoarthritis of the hip or knee" and some of the biologic interventions may be more about prevention of early OA. However, we note that the James Lind Alliance list of top 10 topics includes;

In people with early OA are surgical treatments designed to repair, not replace the joint (such as stem cells, micro fracture and cartilage transplant) effective?
What are the most effective surgical treatments e.g. arthroscopic, biological, realignment, osteotomy in people with early OA?
So we think our proposal matches the JLA priorities, even if it goes a bit beyond the wording in the Commissioning Brief. We would reduce the bid if requested to do so by the HTA Programme. In addition, there are very few treatments that are just preventative- many also provide short and long term effects covering both symptoms and influences on long term structural progression. Meniscal allografts in early OA is an example. So we think it would be better to look at all surgery for early OA, and then see if we can distinguish between effects that might only provide symptomatic relief, and those that may alter the natural history. In practice, it not be possible to separate symptomatic and structural effects, and not entirely necessary - as decision making for arthroplasty is primarily symptomatic, and there is not a good relationship between structural disease and pain.

The fact that this is an HTA call emphasizes the requirement to undertake this research at the current time. Many thousands of hip and knee patients in the NHS with this condition are potentially undergoing ineffective procedures or not undergoing effective procedures. An analysis of the currently available evidence is required to inform treatment guidelines and identify where further research is urgently required.

4. Aims and objectives
Please summarise the key aims and objectives of your project, and provide a concise statement of the proposed research.

Aim
To establish if there is a role for surgery in the management of early osteoarthritis of the hip or knee?

Objectives

1. To undertake an evidence synthesis to determine the clinical effectiveness of currently used surgical interventions for early hip and knee OA, establishing what pre-operative factors have an effect on the outcome or patient experience.

2. A review of safety and adverse events associated with each surgical intervention.

3. Establish the cost-effectiveness of surgical interventions for early knee and hip OA using decision model analysis.

4. To use our results to create clinical treatment guidance for current use of the interventions and to identify areas where new clinical research is required.

M E T H O D S

Evidence Synthesis

This systematic review will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). It will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)[40] The review will be reported in accordance with the PRISMA guidelines[41].

Types of studies

We will start by looking for good quality, recent systematic reviews. Where these exist, we will summarise them and add any new studies published since the review. We may produce new meta-analysis by adding new studies to meta analyses in the reviews. We will include randomised controlled trials and quasi-randomised controlled trials. Cohort studies will be included for long term outcomes (three years or more), further surgery including arthroplasty and revision arthroplasty and adverse event outcomes (for example infections, thromboembolic disease, removal of grafts, 30-day mortality). We will include studies reported as full text, those published as abstract only, and unpublished data. There will be no language restriction.

Our intention would be to exclude studies with fewer than 20 patient per arm, and with duration of follow-up less than 5 years. However based on the volume of good quality evidence, we may need to review these restrictions, particularly on duration. Some shorter-term studies may be useful for hypothesis generation for testing in future trials.

Our scoping searches have found a preponderance of observational studies for some interventions, but a good number of trials for others such as osteotomy. However as anticipated in the commissioning brief, the review will need to include observational studies where RCT data is insufficient.

Setting

The setting will be secondary care for surgical procedures and primary or secondary care for non-operative comparators. -

Target population

We will include adults (18 years of age and older) with diagnosis of early clinical osteoarthritis of the hip or knee joint (ECKOA/ECHOA). We will define ECKOA and ECHOA as:

The presence of joint pain AND one of the following features of structural disease:

Radiographic

Knee:
Kellgren-Lawrence grade 1, 2, 3 or equivalent. Whilst a grade of 3 may be considered moderate OA, it may also be consistent with early OA depending on the precise definition used by the authors, which is not consistent across the literature. We will therefore also plan to include those with the Kellgren Lawrence 3, but consider the exclusion criteria below.

Hip:
Kellgren-Lawrence grade 1, 2, 3 or equivalent, following the same principle as above.
For hip dysplasia – CEA <20
FAI – Alpha angle >55 or centre-edge angle of >40[42]

MRI

Cartilage degradation but minimal full-thickness loss (< 10% of surface area or < 1 cm)
e.g. Boston Leeds Osteoarthritis Knee Score (BLOKS) cartilage morphology[43]
Percent of sub-region surface area affected by cartilage loss (any loss score):
• grade 1: < 10% • grade 2: 10% to 75% • grade 3: > 75%
Extent of full-thickness loss (full-thickness loss score):
• grade 0: none • grade 1: < 10%

OR
Whole Organ Magnetic Resonance Imaging Score (WORMS) cartilage morphology[44]
- grade 1: increased signal from normal-thickness cartilage
- grade 2: partial-thickness focal defect < 1 cm
- grade 2.5: full-thickness focal defect < 1 cm
- grade 3: multiple areas of partial-thickness defect within areas of normal thickness
- grade 4: diffuse partial-thickness loss

OR
MRI Osteoarthritis Knee Score (MOAKS) cartilage morphology[45]
MRI Osteoarthritis Hip score (HOAK)
Size of any cartilage loss as a % of surface area
• grade 1: < 10%
• grade 2: 10% to 75%
• grade 2: > 75%
Extent of full-thickness cartilage loss in a region
• grade 0: < 10%
• grade 1: < 10%
or any equivalent MRI scoring system.

Arthroscopic

Cartilage degradation but no more than one isolated full-thickness defect assessed using the International Cartilage Repair Society (ICRS) score[46]:

- Grade 1: soft indentation (A) and/or superficial fissures and cracks (B)
- Grade 2: lesions extending down to < 50% of cartilage depth
- Grade 3: cartilage defects extending down > 50% of cartilage depth (A) as well as down to calcified layer (B)

OR

an equivalent arthroscopic scoring system such as Outerbridge scale[47].

- Grade 1: Cartilage with softening or swelling
- Grade 2: Partial-thickness defect with fissures on the surface that do not reach subchondral bone of exceed 1.5cm in diameter
- Grade 3: Fissuring to the level of subchondral bone in an area with a diameter greater than 1.5cm
- Grade 4: Exposed subchondral bone

Exclusion criteria
We will exclude participants with the following characteristics:
- Asymptomatic individuals
- End-stage osteoarthritis with full-thickness cartilage loss (> 2 cm), bony deformity or bone-on-bone change on radiographs (Kellgren-Lawrence grade 4).
- Full thickness loss of cartilage in more than one compartment of the joint (knee).

- History of trauma and/or surgery to the knee/hip for fracture
- Inflammatory arthropathy, metabolic bone disease, rheumatoid arthritis

If a study includes a subgroup of participants with EKHOA (as defined above), and these results are reported separately from those with non-early osteoarthritis, then we will include the data that relates to EKHOA only. In the event that a trial appears to have a subgroup of participants with EKHOA but has not reported their results separately, then we will attempt to contact the authors of the trial to ask them to provide the data for the EKHOA subgroup.

Interventions:

1) *Joint preservation – non-regenerative procedures*
(a) Knee.
To include these terms: chondroplasty, radiofrequency, debridement, shaver, meniscal surgery, meniscal debridement, meniscal repair, meniscectomy, meniscal root reconstruction, meniscal root repair.
(b) Hip
To include these terms: osteochondroplasty, radiofrequency, debridement, shaver, labral surgery, labral debridement, labral repair, fibrin glue, reshape, recontour, rim-trim,

2) Joint preservation - Biological reconstruction
(a) Knee
To include the terms: osteochondral grafts, microfracture, AMIC, ACI, MACI, bone marrow concentrates, stem cell concentrates, platelet-rich plasma, meniscal allografts, meniscal implants, membrane, matrix.
(b) Hip
To include the terms: osteochondral grafts, microfracture, AMIC, ACI, MACI, bone marrow concentrates, stem cell concentrates, platelet-rich plasma, labral allografts, membrane, matrix.

3) Joint preservation - Load modifying procedures
(a) Knee
To include the terms: osteotomy, high-tibial osteotomy, distal femoral osteotomy, kine-spring.
(b) Hip
To include the terms: osteotomy, acetabular osteotomy, peri-acetabular osteotomy, Ganz, triple, shelf acetabuloplasty, derotation osteotomy, varus osteotomy, valgus osteotomy

4) *Joint replacement*
(a) Knee
To include the terms: total knee replacement, total knee arthroplasty, partial knee replacement, medial unicompartmental replacement/arthroplasty, lateral unicompartmental replacement/arthroplasty, patello-femoral joint replacement/arthroplasty.
(b) Hip
To include the terms: total hip replacement, total hip arthroplasty, hip resurfacing.

Non-surgical comparator
The comparator will be non-operative conservative management as defined by the NICE Clinical Guideline on Osteoarthritis (CG177, dated February 2014)[10]. This is justified since all individuals with hip and knee osteoarthritis in the UK should be offered NICE recommended interventions, and many of the surgical interventions examined in this review will have been compared to a non-operative comparator, or would have to be if we are to make research recommendations. Accordingly comparators will be included if they consist of one or more of the following 'core' interventions: education and information, activity and exercise, weight loss interventions. Studies will also be included if their non-operative intervention consists a pharmacological management (e.g. NSAIDs, paracetamol, injection therapy), bracing, orthosis and assistive devises, TENS and thermotherapy (heat and ice). Studies will be eligible where these non-operative interventions (defined by NICE as adjuncts) are the delivery alone or in combination with themselves and/or the NICE core interventions.

Types of outcome measures
We will include outcome measures to satisfy the OMERACT and OARSI core outcome set for hip and knee osteoarthritis[48-51] (and the OMERACT Core Outcome Domain Set for joint replacement[51]. These will include clinical outcomes, radiological outcomes and health-economic outcomes.

Clinical Outcomes

1. ***Pain*** measured using a validated pain score. If data on more than one pain scale are provided for a trial, data will be extracted according to hierarchy presented below[52,53]:

i) Pain overall
ii) Pain on walking
iii) Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale
iv) Pain on activities other than walking
v) WOMAC pain subscale
vi) Lequesne osteoarthritis index global score
vii) Other algofunctional scale
viii) Patient's global assessment
ix) Physician's global assessment
x) Other outcome
xi) No continuous outcome reported

2. ***Physical function*** measured with a validated physical function tool. If data on more than one physical function scale are provided for a trial, data will be extracted according to hierarchy presented below[52]:

i) Global disability score
ii) Walking disability
iii) WOMAC functional limitation subscale
iv) Composite disability scores other than WOMAC e.g. KOOS
v) Disability other than walking
vi) WOMAC global scale
vii) Lequesne osteoarthritis index global score
viii) Other algofunctional scale

3. ***Patient reported outcome measures*** (PROMS). We will extract data from validated PROMS for people with hip and knee osteoarthritis, including: WOMAC (Total Score); Oxford Knee Score; Oxford Hip Score; any other validated PROM.

i) ***Patient reported experience measures*** (PREMS) measured using any validated patient reported experience measure.

ii) ***Health Related Quality of Life*** measured using a validated score such as the: EQ-5D; SF-12; or any other validated HRQoL measure.

4. ***Surgical complications and adverse events*** for example infections, thromboembolic disease (DVT/PE), removal of grafts (for some biologics), 30-day mortality.

5. ***Re-operation rate or revision of initial surgical procedure***

6. **Radiological Outcomes**

i) Minimum joint-space width
ii) Median joint-space width
iii) Semi-quantitative measurements, including Kellgren-Lawrence grade or MRI measures.

Health Economic Outcomes

The main health economics outcomes will be quality of life adjusted life years, which when related to costs will provide ICERs. Utilities will be assessed if possible using a generic preference based measure such as EQ-5D. If not we will look for arthritis specific measures from which utility can be derived. For example, it is possible to map from WOMAC to EQ-5D.

Costs will include costs and savings across all NHS and personal care sectors in line with the approach used by NICE. Cost of OP, IP and community care will be obtained from national reference costs, but we will also review previous studies of costs and cost-effectiveness. Discounting of future costs and benefits will be at 3.5% PA.

Minimum duration of follow-up

If multiple time points are reported, we will catagorise them into short- (less than one year), intermediate- (one to three years), and long-term (greater than three years) follow-up. Our intention would be to exclude studies with fewer than 20 patient per arm, and with duration of follow-up less than 5 years. However based on the volume of good quality evidence, we may need to review these restrictions, particularly on duration. Some shorter-term studies may be useful for hypothesis generation for testing in future trials.

Search strategy

We will search the published literature databases: MEDLINE, EMBASE, the Cochrane Library (all sections including CENTRAL and HTA, including the INAHTA database) HMIC, NHS EED (for studies to March 2015), Health Management Information Consortium (via Ovid), and Research Papers in Economics. Embase is particularly useful for conference abstracts. Trial registry and unpublished literature will be searched using the databases: ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and OpenGrey. We will search all databases from their inception to the present, and we will impose no restriction on language of publication. See Appendix 1 for the MEDLINE search strategy. All reference lists from those studies which were judged as potentially eligible on screening will be reviewed. We will also contact all corresponding authors from included studies and ask them to review the included studies for completeness. These two latter stages will provide further assurance that all potentially eligible studies are included in the analysis.

Data collection and analysis

Selection of studies

Two reviewers will independently screen titles and abstracts of all potential studies identify as a result of the search for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication, two reviewers will then independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or by involving additional members of the team if necessary. Multiple reports of the same study will be collated so that each study, rather than each report, is the unit of interest in the review.

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. Two reviewers will independently extract study characteristics from each of the included studies. Any disagreements will be resolved through discussion or by involving additional members of the team if necessary. We will extract the following study characteristics:

1. **Methods:** study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. **Participants:** N, mean age, age range, sex, body mass index, disease duration, severity of condition, comorbidities, socio- demographics, ethnicity, diagnostic criteria, important baseline data, inclusion criteria, and exclusion criteria.
3. **Interventions:** total number of intervention groups within each trial, specific details of each

intervention and comparator. (e.g who provided the intervention, materials used, standardisation of the surgical and non-surgical interventions and adherence to the standardised technique, any modifications or tailoring of the intervention during the trial period.)

4. **Outcomes:** major outcomes specified and collected, and time points reported.
5. **Declarations:** funding for trial, and notable declarations of interest of trial authors.

Two will also independently extract outcome data from included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. We will resolve disagreements by consensus or by involving a third review author. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. Where both final values and change from baseline values are reported for a given outcome, we will extract the final value; if both unadjusted and adjusted values for the same outcome are reported, we will extract the unadjusted value.

Main planned comparisons

We plan to perform the following main comparisons, these will be analysed separately for EKOA and EHOA:

1. Surgical intervention (arthroscopic/open chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus non-operative management following NICE guidance (i.e. combination of information, exercise/physical therapy and weight loss).
2. Surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus non-operative management following a single NICE core therapy intervention (i.e. information or exercise/physical therapy or weight loss).
3. Surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus non-operative management following NICE guidance (i.e. combination of information, exercise/physical therapy or weigh loss) plus one or more additional non-surgical component.
4. Surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus any pharmacological management (e.g NSAIDs, injection therapy).
5. Surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus bracing / orthosis or assistive devices.
6. Surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction and joint replacement) versus electrotherapy (e.g. TENS, thermotherapy).
7. Joint-preserving surgical intervention (arthroscopic chondroplasty or osteochondroplasty, realignment, biological reconstruction) versus joint replacement.

Assessment of risk of bias in included studies

Two reviewers will independently assess risk of bias for each study. For randomised controlled trials, this will be assessed using the Cochrane Risk of Bias tool[54]. Non-randomised studies will be assessed using the Robin-I appraisal tool[55]. Any disagreements by discussion or by involving another team member.

We will grade each potential source of bias as high, low, or unclear risk of bias for the Risk of Bias tool and critical, serious, moderate, low or 'no information' for the ROBIN-I appraisal tool. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will also consider the impact of missing data by key outcomes. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

For quality assessment of RCTs and CCTs, we use the Cochrane Handbook risk of bias (ROB) criteria. These criteria assess the extent to which the design of a study and how that study is conducted is likely to prevent bias (error) in the results. The tool covers six possible biases (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias) which have been shown to reflect the main mechanisms for bias in RCTs[54]. Questions cover the generation of the allocation sequence,

concealment of the allocation sequence, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other threats to validity. The assessment of performance bias, detection bias and attrition bias can be evaluated separately for outcomes that are objective (e.g joint space narrowing) and subjective (e.g quality of life measures). Each criteria is assigned a judgement of "high," "low" or "unclear" risk of bias. Narrative descriptions are also used to provide reasons for a particular judgement. In the review we used the risk of selection bias (generation and concealment of the allocation sequence) to establish the overall risk of bias for each study.

For non-randomised studies we use tools developed by the National Institute for Health, National Heart, Lung and Blood Institute (NIH NHLBI). These tools focus on concepts including biases (selection, performance, detection and attrition), confounding, power and strengths of associations between treatments and outcomes. There are different tools for each major type of study, such as for for cohort studies (two groups), before and after studies (one group), case-control studies (two group studies looking at associations) and case series. Specific guidance notes are provided for each tool. Each question is assigned a response of 'yes', 'no', 'can't determine', 'not reported' or 'not applicable'. The study is then assessed for overall quality (good, fair, poor) based on the responses to the individual questions, where a good study has the least risk of bias, and results are considered to be valid; a fair study is susceptible to some bias but this is not deemed sufficient to invalidate the results; and a poor study indicates that the study is at a significant risk of bias.
Quality scoring involved an element of judgement, because some criteria may be more important than others, and because some criteria may be assessed as not applicable, not reported or can't determine, but as a rough rule of thumb we use the number of "yes" responses:

- For before and after studies, with 10 questions, good 8-10, fair 5-7, poor <5
- For cohort studies with 14 questions, good 10-14, fair 7-9, poor < 7
- For case control studies with 12 questions, good 10-12, fair 7-9, poor <7
- For case series with 9 questions, good8-9, fair 5-7, poor <5.

Quality criteria will be applied by one reviewer and checked by a second reviewer, with disagreement resolved by discussion.

Data analysis and measures of treatment effect

We will undertake meta-analyses only where appropriate based on an assessment of clinical and methodological heterogeneity. Where studies are considered sufficiently homogenous and data are available, meta-analysis will be performed using a random effect model. We will analyse data for each outcome separately for EKOA and EHOA for each of the main comparisons. Statistical heterogeneity will be assessed by visual inspection of the forest plot for obvious differences in results between the studies, and by using the I^2 and Chi^2 statistical tests. If we identify substantial statistical heterogeneity, we will report it and investigate possible causes, and will be reflected in the GRADE assessment.

We will analyse continuous data (such as pain, function, HRQOL, PROMS and PREMS) as mean difference or standardised mean difference (SMD), depending on whether the same scale is used to measure an outcome, and 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect across studies. When different scales are used to measure the same conceptual outcome (for example disability), we will calculate SMDs instead, with corresponding 95% confidence interval. We will back trans-late SMD to a typical scale (for example 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (for example the standard deviation of the control group at baseline from the most representative trial)[56]. We will analyse dichotomous data as risk ratios or Peto odds ratio when the outcome is a rare event (approximately less than 10%), and use 95% confidence intervals. The absolute risk difference will also be calculated using the risk difference statistic and the result expressed as a percentage

If a single trial reports multiple time points for the same outcome, then we will extract the data that relates to the later time point (for example if one trial reports outcomes at six months and one year, we

will extract the one-year results only).

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data (for example when a study is identified as abstract only or when data are not available for all participants). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. Where possible, we will compute missing standard deviations from other statistics such as standard errors, confidence intervals, or P-values[54]. If standard deviations cannot be calculated, they will be imputed (for example from other studies in the meta-analysis).

Assessment of reporting biases

We will create and examine funnel plots to explore possible small-study biases for outcomes where 10 or more studies were included in a meta-analysis. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry[55] and relate this to the results of the review. We will evaluate whether selective reporting of outcomes is present by comparing included study reports with their registered study protocol when available through the ClinicalTrials.gov or WHO International Clinical Trials Registry platforms.

Data synthesis

Subgroup analysis and investigation of heterogeneity

Where sufficient data are available, we plan to carry out the following subgroup analyses for outcomes related to patient-reported pain and function:

1. Age 18 to 40 years, 40 to 50, 50-60, 60-70, 70-80 and >85.
2. Gender
3. Grade of structural disease determined by Kellgren-Lawrence grade
4. Surgical approach (for osteochondroplasty of the hip only)

Sensitivity analysis

Where sufficient data are available, we plan to carry out sensitivity analyses examining the effects of quality criteria:

1. including missing or inappropriately analysed data;
2. including trials with unclear allocation concealment (at risk of selection bias);
3. including trials with an incomplete description of EKOA or EHOA;
4. including trials at risk of detection bias (i.e. unclear or no blinding of participant for participant-reported outcomes).

Summary of findings tables

We will produce 'Summary of findings' tables (showing the results separately for hip and knee procedures) based on each of the four main groups of surgical interventions (arthroscopic chondroplasty, osteotomy, biological reconstruction and joint replacement) compared to non-operative management following NICE guidance (i.e. combination of information, exercise/physical therapy and weigh loss).

We will use the GRADE approach using GRADEpro software (i.e. study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes.

Heath economic modeling
Economics

Decision-analytic models for early hip and knee OA will be developed to assess the cost-effectiveness of the treatment alternatives considered in this proposal and evaluate which represents best value for money: (a) Non-operative conservative management, (b) Arthroscopy, (c) Osteotomy, (d) Biological reconstructions, and (e) Joint replacement. We will conduct cost-utility analysis to assess cost-effectiveness in terms of the cost per quality-adjusted life-year (QALY) gained from the perspective of the UK National Health Service, including personal and social services costs if sufficient data exist. Separate models will be developed for each joint to reflect the fact that interventions, clinical management and data inputs are different for each joint, as described in previous sections. The models will be informed by reviews of published economic evaluations and findings of the clinical effectiveness reviews detailed in the previous sections and supplemented by expert clinical opinion. We will follow best practice guidelines for modelling techniques applied to the evaluation of interventions to inform healthcare decisions.

Economic evidence review

- Model will be populated with findings from clinical and economic reviews and expert opinion
- Building on previous reviews from Warwick (ACI, allografts, hip replacement and hip resurfacing)
- Same methods as clinical effectiveness
- Include full economic evaluations
- Focus: to identify pertinent modelling methodologies which help develop a *de novo* model to address our specific decision question

Model structure

- We will build on previous experience from economic models developed by members of the health economic team (total versus partial knee replacement, autologous chondrocyte implantation in the knee, cost-effectiveness of different knee prostheses, etc)
- To be determined based on relationship between patient characteristics and main outcomes, as well as data availability
- Options are microsimulation (patient-level, discrete event simulation) and cohort model simulation (Markov model) Or combined Markov and decision tree?. Starting age 30 and starting point an OA risk factor such as dysplasia, meniscectomy, injury
- Criteria for the choice: if patient history affects the incidence of key events and outcomes, and survival data are available for these, then patient-level; if either of these fails, then Markov
- Developed by research team based on findings of evidence synthesis of clinical effectiveness, review of associated safety and adverse events, and discussions with relevant clinical expert co-applicants
- Specific interventions will be those described in specific section supra
- Key events include re-operations, adverse events, return to work/sport
- Time horizon: lifetime, although might consider shorter time horizons if considered meaningful or useful to decision-makers Life time better because the need for revision THR and TKR is important economically if first THR/TKR is early
- Based on hypothetical individuals or cohorts undergoing the interventions
- Structure to be presented and agreed at Advisory Group meeting
- Discounting at 3.5% with SAs other rates??

Model inputs

- Model will be primarily populated with findings from clinical and economic reviews and expert opinion
- The use of data from observational studies will be required in cases where RCT is not available

- Javlin, an observational study exploring new cost effective ways to follow-up patients after surgery, where extended use of patient related outcome scores across the entire pathway plays a key role. (A Price)
- The Multicenter Osteoarthritis Study (MOST), "a longitudinal, prospective, observational study of knee OA in older Americans with OA disease or at increased risk of developing it."
- The Osteoarthritis Initiative, an American research study, sponsored by the National Institutes of Health, aimed at better understanding how to prevent and treat knee osteoarthritis
- Natural history studies of untreated lesions such as OCD and after meniscectomy

• Quality of life outcomes

- Heath utilities derived from EQ-5D, SF-12, or any other validated HRQoL measure to obtain QALYs
- Pain, discomfort, functioning scales that may be mapped to EQ-5D

• Reoperation rates especially revision of TKR, UKR/TKR

• Adverse events. One thing which never I have never seen in modelling of OA is impact of activity or inactivity on CVD or T2DM risk. Probably worth mentioning but not attempting to model? Can discuss. Would this include infections?

• Costs

- Inpatient
- Outpatient including rehab services primarily physio
- Primary care (consultation and prescriptions). Some get considerable pain, need powerful analgesics such as tramadol, and addition is a risk?
- Productivity loss: Return to work. Relevant, but subject to data being available
- Return to sport is a common indicator in younger people

Subgroups

• We will consider subgroup analysis or evaluation of heterogeneity if data permits, taking account of aetiologies such as hip dysplasia, post-meniscectomy

• Age 18 to 40 years, 40 to 50, 50-60, 60-70, 70-80 and >85.

• Gender

Sensitivity analysis

• One- or two-way sensitivity analysis on key parameters

• Probabilistic sensitivity analysis

- To characterise the impact of model parameter uncertainty on deterministic results and estimate cost-effectiveness acceptability curves

Results

• Main outcome: cost per QALY gained for each intervention/comparator pair

• CEACs from probabilistic sensitivity analysis

• Expected value of perfect information will be used to estimate the cost of the model parameter uncertainty as a guide for potential future areas of research

6. Outputs, Dissemination and anticipated Impact

Outputs from this research will include:
(1) A written HTA report published through the NIHR library
(2) 8 separate publications with Evidence synthesis for the use of the following procedures for surgical treatment of early hip (4) and knee (4) OA: (A) Arthroscopic interventions, (B) Osteotomy realignment procedures, (C) Biological reconstruction techniques and (D) Joint replacement.
(3) Identification of further research needs where clinical and cost efficacy uncertainty exists – leading to NIHR call for research.
(4) Development of treatment guidance where appropriate – working with BASK, BHS and the BOA.

We will pursue an active Dissemination of the evidence produced:
(1) Present the outputs of this work at National and International meetings.
(2) Summary of outputs shared with Orthopaedic community through BASK, BHS and BOA membership email communication.
(3) Article in BOA news.
(4) Review article in British Bone and Joint Journal
(5) Press release working with NDORMS communication team.
(6) Patient facing project specific information website hosted at NDORMS.

Impacts will include;
(1) Changes in current NHS practice – supporting the use of interventions that are effective and produce value for patients. At the same time reducing the use of ineffective procedures, reducing patient's exposure to unnecessary surgery and saving the NHS money.
(2) Calls for further research – where new evidence is required funding will be required through NIHR and other funding bodies
(3) Generation of future evidence

There are no regulatory or IP barriers regarding this research programme.

7. Project / research timetable

The project will be completed over a 20-month period. The key milestones are presented in the chart below.

Task	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Evidence synthesis																				
Protocol development	■																			
Searches	■	■																		
Screening and study selection	■	■	■	■																
Data extraction, quality assessment, checking				■	■	■	■													
Synthesis (metanalysis)						■	■	■	■	■	■	■								
Health economics																				
SR of previous HE literature			■	■	■	■														
Data extraction, quality assessment, checking					■	■	■	■												
HE model development								■	■	■	■	■	■	■						
Model results													■	■	■	■	■			
Outputs																				
Present at meetings																	■	■	■	■
Paper writing																	■	■	■	■
Report writing																	■	■	■	■

8. Project management

All project proposals should include details of how the project will be managed. For projects involving a number of institutions or component parts, effective project management is essential to ensure the work is completed within the planned timeframe. You should set out how joint applicants in different institutions will communicate and monitor progress of the project.

This program of research is collaboration between the University of Oxford and the University of Warwick with work being carried out in both sites.

The Project Management Group will consist of representatives from both centres and will meet bi-monthly in face-to-face cross site meetings. The PMG will be chaired by Andrew Price, with Norman Waugh leading for Warwick. The PMG will receive updates from the Evidence Synthesis Group (Sally Hopewell Lead) and the Health Economic Analysis Group (Rafael Pinedo-Villaneuve Lead). The PMG will work to ensure that the project milestones are met and monitor the day to day running of the project.

The Evidence Synthesis Group (ESG) will be led by Sally Hopewell (SH) and will include Toby Smith (Oxford), Norman Waugh (Warwick) and Carol Royle (Warwick), tighter with 2 systematic reviewers under supervison of SH> in Warwick, who will run all searches once agreed by the ESG. Evidence synthesis will be shared between sites with Oxford leading on (A) Arthroscopic osteochondroplasty and meniscal/labral surgery, (B) Load redistribution procedures and (C) Joint replacement. Warwick will perform the evidence synthesis of (D) biological repair techniques, as they have considerable experience in this area from previous HTA and NICE related work. The ESG will meet via video conferencing bi-weekly.

Health Economic Group will be led by Rafael Pinedo-Villaneuve (RP-D) and will include Hema Mistry (Warwick), Helen Dakin (Oxford) and Alastair Gray (Oxford), together with HE researcher employed to carry out the analysis work under RP-D's supervision. The HEG will meet via video conferencing bi-weekly.

A Steering Group will be created with an independent chair-person and 2 other external members, together with entire study team. The SG will meet three times; once at the beginning of the study, once at the end of the first year and lastly towards the end of the second and final year The aim of the SG will be to monitor progress of the project.

9. Ethics

There are no requirements for ethically review as the work is based on evidence synthesis of previously published work.

10. Patient and Public Involvement

There has been significant patient and public involvement in the generation of this research project. This HTA call for research is based around the output for the James Lind Alliance Priority Setting Partnership (JLA PSP) on Surgical intervention is early hip and knee OA. This PSP was initiated by Professor Andrew Price and based in Oxford. We initiated the work to ensure a significant role for patients and the public in setting the research agenda around this clinical area. All the research questions were in part produced or modified by patients and the public.

The HTA used the JLA PSP to create this call for Evidence Synthesis and Health Economic decision analysis modeling in the clinical area of early hip and knee OA. In developing this application we have worked with a patient and public representative who was one of the original PP members of the JLA PSP. We have done this to maintain PPI continuity with the PSP during the development of our research program. Fraser Old is a very experienced patient and public representative in MSK

research projects. He has been integral to the production of this application working with active involvement in planning the work as a co-applicant.

If we are successful in gaining funding to carry out our research Fraser Old will continue his involvement in the research project, sitting on the Steering Group and the Project Management Group. He will also have an active involvement in the engagement with the wider patient and public body via planning content for our patient facing website and supporting our patient open days where research findings are disseminated.

We follow INVOLVE guidelines for the payment and recognition of PPI services.

11. Project / research expertise

The project is collaboration between the Universities of Oxford and Warwick, with a significant body of experience in the clinical area under investigation and the research methods in Evidence Synthesis and Health Economic Modeling required to plan, perform, report and disseminate the research in surgery for early hip and knee OA that has been commissioned.

Professor Andrew Price (Oxford)(PI)
Academic Orthopaedic surgeon with clinical practice and history of research focused on the treatment of early knee OA. Previous HTA programme grant PI. Instigated and led the JLA PSP on early knee OA and Cochrane Review on surgical treatments for early knee OA. He will be PI of the entire study, coordinating work and chairing the Study Management Group.

Mr. Fraser Old
A previous patient with early and late stage hip and knee OA. Extensive experience as a patient representative in research and a member of the steering committee for the James Lind Alliance PSP focused on Early Knee and Hip OA. He will be an active member of the research team sitting on the Study Management Group and the Steering Group.

Associate Professor Andrew Metcalfe (Warwick)
Academic Orthopaedic surgeon with clinical practice and history of research focused on the treatment of knee OA. Specific interest in systematic review and evidence synthesis - recently involved in HTA report for NICE for ACI treatment. He will co-ordinate the study work in Warwick, offer clinical insight to the knee surgery analysis and will be a member of the SMG.

Professor Sion Glyn-Jones (Oxford)
Academic Orthopaedic surgeon with clinical practice and history of research focused on hip OA. He is PI for the FAIT trial of surgery for FAI and has a specific interest in new treatments for early hip OA treatment. He led hip clinical input to the JLA PSP on early hip/knee OA. He will provide clinical insight in to hip surgery analysis and will be a member of the Study Management Group

Mr. Peter Wall (Warwick)
Academic Orthopaedic surgeon with clinical practice and research focused on the treatment of early hip OA and FAI surgery. He will provide clinical insight into hip surgery analysis in Warwick.

Associate Professor Sally Hopewell (Oxford)
Based at the Centre for Medical Statistics she is an expert in systematic review and evidence synthesis. She previously worked at the UK Cochrane Centre and has published widely including reporting guidelines. She will lead evidence synthesis in Oxford, supervising the two Oxford based systematic reviewers in the project. She will be a member of the Study Management Group.

Dr. Toby Smith (Oxford)

A senior researcher in rehabilitation with expertise in the non-operative treatment of early OA, systematic reviews and epidemiology. He will assist in advising and analysis of control data regarding non-operative NICE guidance OA treatment.

Professor Norman Waugh (Warwick)
Expert in Evidence Synthesis and Health technology Assessments of treatments and medical technology. Has completed over 40 HTA evidence synthesis publications and has performed work for NICE, the National Screening Committee and the Department of Health. He will lead evidence synthesis at Warwick and be a member of the Study Management Group.

Dr. Rafael Pinedo Villanueva (Oxford)
Health Economist and University Research Lecturer at the Nuffield Department of Orthopaedics, Rheumatology and MSK Science. Expert in decision analysis modeling relating to MSK conditions, including osteoarthritis and surgical interventions. He will lead the HE analysis group involved this project and will supervise the HE researcher based in Oxford. He will be a member of the Study Management Group.

Dr. Helen Dakin (Oxford)
A senior researcher at the Health Economic Research Centre based at the Nuffield Department of population health. Expert in decision analysis modeling relating to MSK conditions, particularly hip and knee surgery for OA. She will support the Oxford HE analysis working as part of the HE analysis group.

Professor Alastair Gray (Oxford)
Director of the Health Economic Research Centre based at the Nuffield Department of Population Health in Oxford. Vast experience in HE decision-analytic modelling methods to estimate the likely cost-effectiveness of new and existing health care interventions. He will provide senior support to the HE analysis group.

Mr Antony Palmer (Oxford)
Clinical Lecturer in Orthopaedic Surgery with specific clinical interest in imaging of early OA treatment, together with development and investigation of new treatments. He will play a specific role in coordinating the Study Management Group.

12. Success criteria and barriers to proposed work

We will use the following measures of success:
1. Meeting our milestones during the program.
2. Completing and submitting the HTA report for publication.
3. Publication of all eight papers that are generated from the program.
4. Presentation of the work at a least one national and one international meeting
5. Creation of at least 2 treatment guidelines endorsed by the BOA.
6. Identification of new research needs in this area that generate at least 2 new NIHR funding opportunities over the next 3 years.

We do not envisage any significant risks to this research, as the work is it is evidence synthesis and health economic analysis of existing data. The only practical issue will be where not enough evidence exists to generate clinical guidelines, but in these case new research priorities will be generated instead.

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