MOTION Trial Protocol

Version 1.0 13th October 2022

What is the clinical-effectiveness and cost-effectiveness of surgery with medial opening wedge high tibial osteotomy (HTO) compared with non-surgical treatment in the management of osteoarthritis (OA) of the knee in patients younger than 60 years? (MOTION Trial)

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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ACL	Anterior Cruciate Ligament
CEAC	Cost-Effectiveness Acceptability Curve
CI	Chief Investigator
CRF	Case Report Form
EQ-5D	EuroQol 5 Dimension Health Survey
ECTU	Edinburgh Clinical Trials Unit
FJS	Forgotten Joint Score
GCP	Good Clinical Practice
HCRU	Health Care Resource Use
HTO	High Tibial Osteotomy
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
JLA	James Lind Alliance
KOOS	Knee Osteoarthritis Outcome Score
MRAV	Minimum Requirements /Acceptable Variation (proforma)
NICE	National Institute for Health and Care Excellence
NJR	National Joint Registry
OA	Osteoarthritis
OKS	Oxford Knee Score
PKT	Personalised Knee Therapy
PCL	Posterior Cruciate Ligament
PI	Principal Investigator
PROM	Patient Reported Outcome Measure

PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
TKR	Total Knee Replacement
QA	Quality Assurance
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
SOP	Standard Operating Procedure
UKKOR	United Kingdom Knee Osteotomy Registry

1 INTRODUCTION

1.1 BACKGROUND

Osteoarthritis (OA) of the knee is a degenerative joint disease which causes knee pain and disability. The options for treatment are either non-surgical (counselling, painkillers, physiotherapy, walking aids, steroid injections) or surgical. In patients >60 years with disabling knee OA, surgery with knee replacement (partial or total) where the joint is excised and replaced with an artificial metal/plastic implant, has been proven to be successful. However, in patients <60 years knee replacement is not as successful and is associated with a higher failure rate, poor patient reported outcome scores and an earlier requirement for redo-knee replacement (7,8,9,10,11). Realignment of the lower leg with a procedure called high tibial osteotomy (HTO) has shown promise by relieving pain and improving function in patients with knee OA (1,2). A wedge is opened just below the knee to realign the entire lower leg in a manner so that the weight-bearing axis (hip to ankle) passes through the middle part of the knee away from the diseased and arthritic inner half of the knee (Figure 1). Since the native knee joint is preserved in HTO, it is a desirable surgical option in active patients <60 years with the aim of avoiding knee replacement altogether or delaying the need for knee replacement until they are >60 years, when results become more predictable. Published data suggests that surgical treatment of knee OA with HTO avoids the need for a knee replacement in around 90% of patients for 5 years and 70% of patients for 10 years after the operation (1,2). However, the clinical and cost effectiveness of surgical treatment with HTO has never been compared with non-surgical treatment in patients <60 years with knee OA. This trial is aimed at filling this evidence gap.

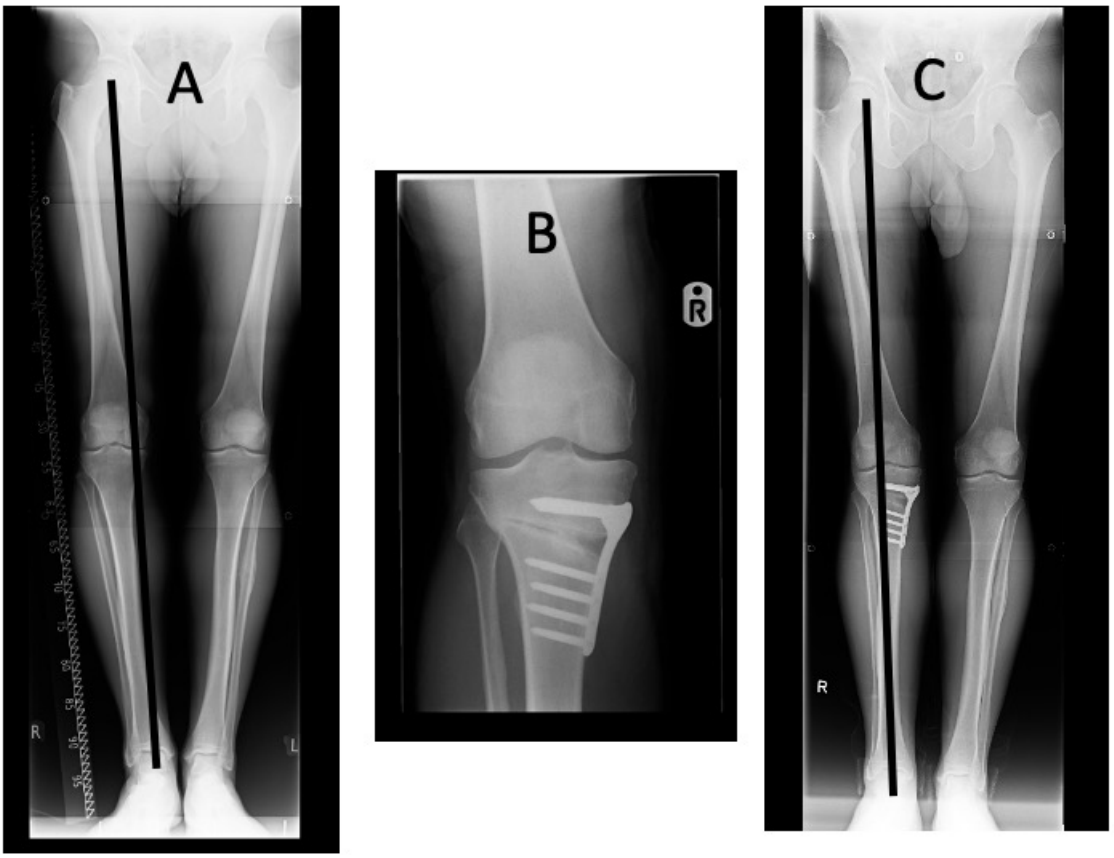


Figure 1: A. The black line is drawn from the centre of the hip to the centre of the ankle and represents the weight-bearing axis (how the body weight passes through the leg). Normally this weight-bearing axis should pass through near the middle of the knee. In this patient suffering from knee OA the weight- bearing axis is abnormal and passes through the inner diseased half of the knee instead of near the middle of the knee **B:** A wedge has been opened just below the knee joint and stabilised with plates and screws in the operation called high tibial osteotomy (HTO). By opening this wedge of bone, the overall alignment of the lower leg and its weight-bearing axis is altered as shown in **C.** The lower leg has been realigned so that the weight-bearing axis (black line) now passes through the middle of the knee, away from the diseased inner half of the knee. This shifting of the weight-bearing axis away from the arthritic inner part of the knee following HTO relives pain and reduces disability with preservation of the native knee joint.

1.2 RATIONALE

1.2.1 Intervention – High tibial osteototmy

A. Rationale: The standardisation of the surgical technique with the so-called 'medial-opening wedge' HTO has permitted controlled measured deformity corrections, secure fixation with locked plates and quicker rehabilitation. These advancements addressed previous shortcomings of the technique which has now remained stable for the past 15 years (1,2,12,16,18,19, 20). In 2021, a consensus document was published in the UK regarding indications for surgery, decision making, surgical planning, technique, post-operative assessment and recovery. The consensus statements were formulated by a panel of 29 UK based knee surgeons who regularly undertake osteotomy (61). The following key consensus statements (61) support the rationale for the MOTION trial:

1. Kellgren Lawrence Grade 4 (bone on bone) unicompartment arthritis is not considered to be a contraindication to osteotomy.

2. Bipodal weight-bearing long leg alignment imaging should be performed in all cases prior to osteotomy. The mechanical axis of the femur and tibia should be calculated in each case and the site of osteotomy individualised based on the deformity present. This can be undertaken using standard digital imaging software or dedicated osteotomy planning software

3. Prior to performing osteotomy an MRI scan of the knee is recommended to assess the entire knee and the suitability for osteotomy. It is not essential to perform a concurrent arthroscopy. However, if arthroscopy is performed osteotomy can still proceed when appropriate, in patients with grade IV degeneration within the patellofemoral joint.

4. The planned osteotomy method and correction point is dependent on the indication and the severity of the disease. It should be individualised with the general aim of shifting the mechanical axis out of the diseased compartment.

B. Risks: The surgery is associated with general risks including infection, bleeding, neuro-vascular injury and thromboembolic complications. Procedure related risks include intra-operative fracture, non-union of osteotomy, under/overcorrection and conversion to knee replacement. Overall, major complications and severe adverse

events following the modern HTO are now much lower than previously reported with rates between 5%- 10% in the published literature (1,2,18,19,20).

C. Review of evidence – High tibial osteotomy (HTO): A Cochrane review identified 21 randomised studies examining HTO in 1065 patients (1). The mean number of participants in the 21 studies was 52 (range 30-100) and mean age was 60 years (range 42-67 years). None of these studies compared HTO with non-surgical treatment. 19 studies compared different HTO techniques and 2 compared HTO and partial knee replacement. HTO reduced pain and improved knee function in patients with knee OA. However, this conclusion was based on within-group comparisons, and not on non-operative controls. The two studies comparing HTO and partial knee replacement reported no significant differences between the treatments at 7.5 years in terms of treatment failure (risk ratio=1.32, 95% confidence interval (CI) 0.84-1.87) and pain/functional outcome (precise treatment effect not estimable). However, a probabilistic analysis of systematic review data at 10 years following surgery found that HTO was most likely to be cost-effective in patients <60 years and partial knee replacement in patients >60 years (12). Registry data on 3195 HTOs performed between 1987-2008 in Finland demonstrated that 89% (95% CI 88 to 90) did not need a knee replacement within 5 years and 73% (95% CI 72 to 75) did not need one within 10 years (2). Such longer-term survival and satisfactory patient reported outcomes after HTO have also been reported in a recent systematic review of HTO, but the same review also recognised the lack of high-quality studies investigating HTO (22). Finally, HTO does not compromise the later requirement for knee replacement. Joint registry data from Denmark (20) has shown that, when corrected for age and gender, the 10 year survival of knee replacement is not significantly worse when performed after HTO (n=1044) compared to without prior HTO (n= 63,763): 91% compared to 94% (hazard ratio 1.19, p=0.09).

1.2.2 Comparator – Non-surgical treatment (Personalised Knee Therapy, PKT)

A. Rationale: The MOTION non-surgical intervention is a specialised package of knee rehabilitation and represents physiotherapist-led best-care for medial compartment knee OA. It is based on best-practice guidance and was developed with a team of physiotherapy academics from Edinburgh Napier University and clinical specialist physiotherapists from NHS Lothian following an evidence review and with considerable PPI involvement throughout. Our PPI group reviewed the proposed rehabilitation package and considered it to be very different from the physiotherapy they may have received in the community before referral to secondary care. This package of 'Personalised Knee Therapy' (PKT) has also been 'road-tested' at the lead site by the co-applicant (DH) as part of the development of the MOTION trial drawing on the experience of delivering non-operative interventions in multi-site clinical trials in the UK (32,35). Patients were particularly keen to ensure a comprehensive non-operative intervention that is distinct from any previous therapy they may have received earlier in the disease process (prior to referral to secondary care). A core package will deliver (a) progressive structured exercise programme (b) advice on lifestyle, pain management and (where appropriate) weight management. There will be an optional inclusion of biomechanical interventions (bracing or insoles), manual therapy, steroid injection and treatment of additional co-existing symptoms (that interact with and exacerbate the knee symptoms) where this falls within local usual care. The intervention will be delivered over 6 outpatient contact sessions with a specialist physiotherapist over a period not exceeding 4 months.

B. Risks: The risks with non-surgical intervention are much less compared to the surgical intervention but include pain exacerbation from exercise therapy, steroid induced pain exacerbation or joint infection and skin breakdown from brace/orthotic usage.

C. Review of evidence - Non-surgical treatment: The NICE clinical guideline CG177 emphasises a holistic approach to non-surgical management that includes non-pharmacological treatments, pharmacological treatments and steroid injections (4). A Cochrane review of the effectiveness of exercise alone in knee OA concluded that high-quality evidence indicates that land-based therapeutic exercise provides short-term benefit that is sustained for at least 2-6 months after cessation of formal treatment in terms of reduced knee pain, and moderate-quality evidence showing improvement in physical function among people with knee OA (23). Recent systematic reviews from international patient and public organisations dedicated to improving the treatment of OA have also provided substantial evidence to suggest moderate effectiveness of non-surgical treatment for knee OA (24,25,26). In a randomised trial published this year, patients with knee OA who underwent physiotherapy had less pain and functional disability at 1 year than patients who received an intraarticular glucocorticoid injection (27). A Danish randomised controlled trial (100 patients) compared the efficacy of a 12-week non-surgical treatment program with 'usual care' in patients with knee OA (28). The treatment program consisted of individualized progressive neuromuscular exercise, patient education, insoles, dietary advice and analgesics, while usual care comprised two leaflets with information and advice on knee OA and recommended treatments. Compared with usual care, patients undergoing the treatment program improved more in the Knee injury and Osteoarthritis Outcome Score (KOOS) adjusted mean difference 9.6 (95% CI, 4.4-14.8, MCID 8-10). In a second randomised controlled trial, the same research group found that 66% of patients receiving the intervention chose to delay knee replacement for at least 2 years (29). Around 12,796 patients with knee OA have now taken part in a tailored non-surgical management program of exercise and education in Denmark. This was found to be effective in reducing pain by 13.4 points (95% CI; 9.7 to 17.1) on a 0-100 scale (30). Finally, local data from Edinburgh (lead centre) indicates that initial non-surgical management of symptomatic knee OA in primary care fails to meet minimum treatment guidelines in the vast majority of patients and suggests that a tailored approach may be more successful in delaying the need for knee replacement (31,32).

1.2.3 Why this research is needed now, with reference to current NHS policy/practice

Our proposal is timely because both the number of patients with knee OA and the average life expectancy is expected to increase dramatically over the next decade, and the enormous health and economic burden of surgically treating knee OA has now been recognized by the NHS and worldwide (3,4,33). The uncertainties in relation to the optimal treatment options detailed in this proposal have also been recognised by the James Lind Alliance (JLA) which has designated the surgical and non- surgical options for the treatment of knee OA as a Top 10 Priority Setting Partnership in 2016 (34). The research questions we have formulated for this proposal are directly aligned to JLA surgical priorities 1,4, 5, 6, 7 and 10, JLA non- surgical priorities 1,2,3 and 6 and JLA other important priorities 2 and 3 (www.jla.nihr.ac.uk/priority-setting-partnerships/early-hip-and-knee-osteoarthritis/top-10-priorities.htm). This study has the approval of the British Association for the Surgery of the Knee (BASK; www.baskonline.com).

2 STUDY OBJECTIVES

2.1 OBJECTIVES

The objective of this trial is to conduct a pragmatic, multicentre, randomised controlled trial to determine whether the intervention is superior to comparator by answering the following two research questions:

(1) For patients <60 years with medial compartment knee OA, what is the relative clinical effectiveness (pain relief, improvement in function, quality of life, return to work) of HTO compared with non-surgical management at 24 months?

(2) For patients <60 years with medial compartment knee OA, what is the relative cost-effectiveness of HTO compared to non-surgical management at 24 months and as modelled over a lifetime horizon?

2.2 ENDPOINTS

The primary and secondary endpoints will be captured within the following framework: **Population** - NHS patients <60 years with symptomatic knee OA localised to the medial compartment in whom surgical intervention is indicated. **Intervention** - Surgery with medial opening wedge HTO followed by standard postoperative rehabilitation based on local pathways. **Comparator** - Non-surgical intervention with Personalised Knee Therapy (PKT) delivered within an NHS physiotherapy department.

Primary endpoint

The primary outcome is the composite 24-month Knee Injury and Osteoarthritis Outcome Score (KOOS) score (www.koos.nu).

Secondary endpoints

1. Minimum requirements/acceptable variation (MRAV) proforma completed between 6 -12 months post intervention (note that this interval may be different from the same period post-randomisation due to NHS waiting lists)

2. KOOS composite score 12 months post-randomisation.

3. Five separate KOOS subscales at 12 and 24-months post randomisation.

4. Oxford Knee score (OKS, www.innovation.ox.ac.uk) at 12 and 24- months post-randomisation (46).

5. Forgotten Joint Score-12 (FJS-12, www.forgotten-joint-score.info) at 12 and 24-months post-randomisation (47,48).

6. EuroQol EQ-5D-5L score (EQ-5D-5L – EQ-5D (euroqol.org))(49)

7. Pittsburgh Sleep Problem Scale at 12 and 24-months post randomisation (32)

8. Return to Work/Employment Questionnaire (9,10).

9. Additional study-knee related operative intervention at 12 and 24-months post randomisation

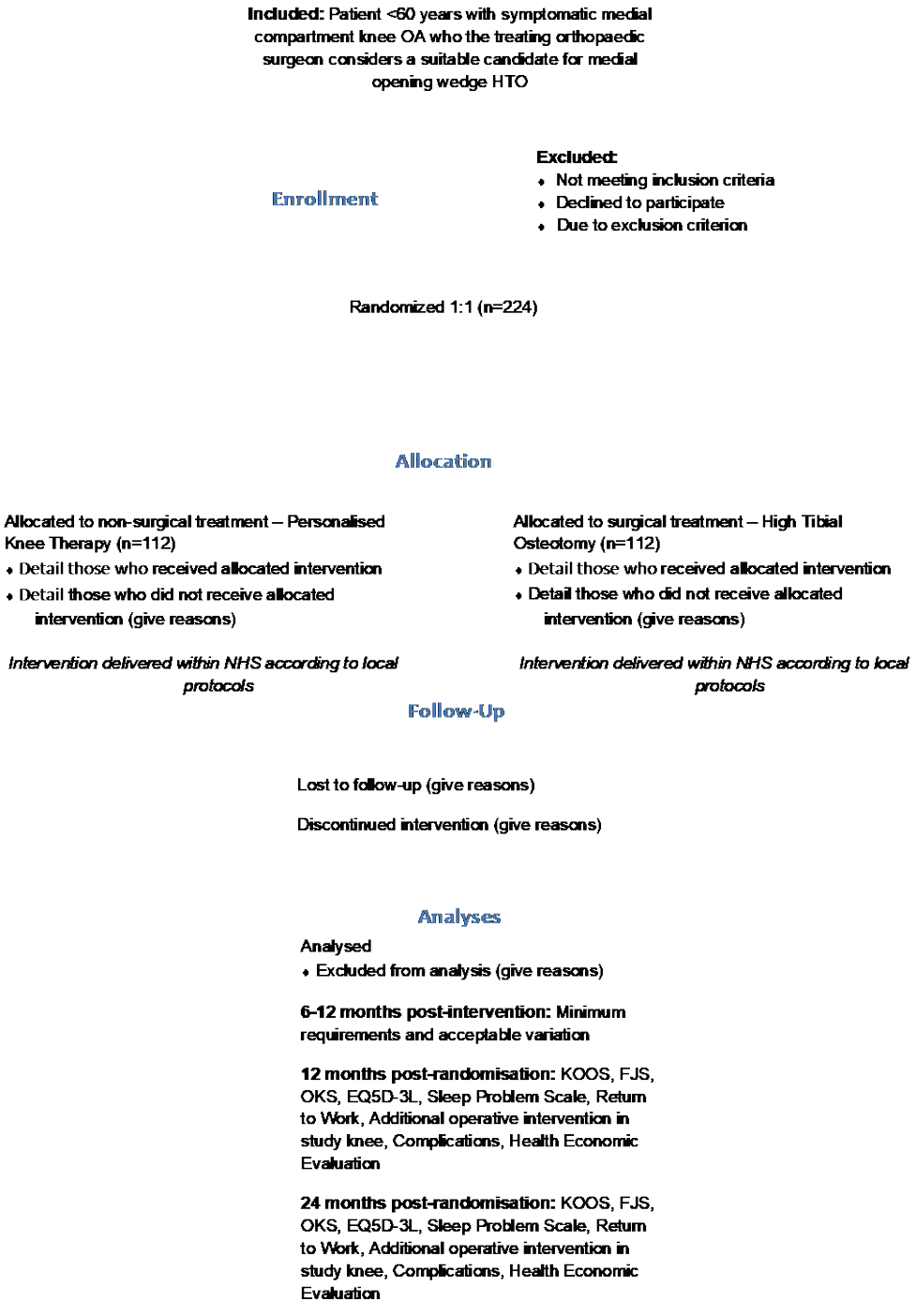
10. Intraoperative and postoperative complications 12 and 24 months post-randomisation

11. Health Economic Evaluation Outcomes

a. Health and social care resource utilisation and associated NHS and PSS cost and Quality Adjusted life years (QALY) at 24 months
b. Incremental Cost per QALY at 24 months
c. NHS and PSS cost, and QALYs as modelled over a lifetime horizon to account for future impacts on the need for TKR and associated revision surgery and their timing relative to retirement
d. Incremental Cost per QALY as modelled over a lifetime horizon to account for future impacts on the need for TKR and associated revision surgery and their timing relative to retirement.

3 STUDY DESIGN

MOTION is a multi-centre, prospective randomised open blinded endpoint (PROBE) parallel-group controlled trial. Patients will be randomly assigned to one of the two treatment arms, in a 1:1 ratio, centrally, by the Edinburgh Clinical Trials Unit (ECTU) via a web-based system. To ensure groups are balanced, a minimisation algorithm will incorporate age, sex, body mass index and baseline KOOS score. Patients will be randomised to either the surgical intervention of High Tibial Osteotomy (HTO) or non-surgical intervention of Personalised Knee Therapy (PKT).



The setting will be within the orthopaedic surgical departments of NHS hospitals in the UK that treat patients with medial compartment knee OA with facilities to support the trial. Patients will be followed up for 24 months following recruitment. The study design incorporates a 9-month internal pilot which will be reviewed by the Data Monitoring Committee (DMC), Trial Steering Committee (TSC) and the funder to determine whether the study progresses to the full trial. We plan to open at least 5 sites during the pilot phase (see Table 1 below). An embedded process evaluation will record specific factors affecting the recruitment rate to provide further data to optimise recruitment. Following the pilot and meeting the stop / go criteria additional sites will be invited to participate.

Table 1: Stop/Go criterion for Internal pilot phase

Progression Criterion – Internal pilot	**Red**	**Amber**	**Green**
Trial recruitment			
Number of sites opened during pilot	2 or less	3-4	>5
Total number of participants recruited	<10	10-20	>20
Recruitment rate/site/month	<0.2	0.2-0.7	>0.7
Non-adherence			
Cross-over rate (%)	>50%	20-50%	<20%
Off-protocol intervention rate (%)	>30%	10-30%	<10%

4 STUDY POPULATION

4.1 Number of participants

A total of 224 patients (112 in each arm) will to be recruited from approximately 20 UK sites over a 24-month period.

4.2 Inclusion criterion

Patient <60 years with symptomatic medial compartment knee OA who the treating orthopaedic surgeon considers a suitable candidate for medial opening wedge HTO

4.3 Exclusion criterion

1. Age <18 years or >60 years
2. Body mass index (BMI) >40
3. Patients considered for HTO but who DO NOT have any knee OA including:
    a. Offloading HTO for concomitant cartilage repair (No OA)
    b. Offloading HTO solely to treat ligamentous instability (ACL/PCL)
    c. Symptomatic avascular necrosis/osteonecrosis
    d. Correction of intraarticular or extraarticular post-traumatic knee deformity
4. Patients requiring double-level knee osteotomy for correction of deformity
5. History of inflammatory arthropathy including rheumatoid arthritis, ankylosing spondylitis, gouty arthropathy and psoriatic arthropathy
6. Previous high tibial or distal femoral osteotomy in same or contralateral knee
7. Previous knee replacement (partial or total) in the same or contralateral knee
8. Cognitive impairment resulting in the inability to consent.
9. Inability to comply with study procedures.
10. Previous history of septic arthritis in the knee

4.4 Co-enrolment

Should the need for co-enrolment arise, the sponsor policy in relation to co-enrolment will be followed . This can be viewed at the following website link: www.accord.scot/sites/default/files/POL008%20Co-enrolment%20v2.0%20-%20signed.pdf

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 Identifying participants

Potential patients will be identified and approached in outpatient or specialist knee clinics by the usual care team comprising the participating surgeon or their delegated specialist trainee. Patients will be provided with the MOTION Patient Information Sheet & Consent Form (PISCF) (Appendix 1) and asked if they are willing to be contacted by the local research team using a 'MOTION Consent to contact' form (Appendix 2). If so a screening visit to assess their eligibility for the study will be arranged. If the patient is identified during an outpatient appointment this screening visit could coincide with their outpatient clinic appointment, depending on local circumstances.

5.2 Consenting participants

Participants meeting the inclusion and exclusion criteria will be approached for consent by a member of the research team delegated to take consent allowing sufficient additional time to consider the study information. Following consent, data will be collected to allow randomisation. The trial consent form is detailed in Appendix 1.

There is provision within the trial consent form to request patient consent for longer term follow-up at 5 and 10- years post-intervention through data linkage, to measure survivorship of HTO and later requirement for knee replacement.

This will be a separate study and additional funding to conduct the study will need be sought.

The trial also incorporates a process evaluation (please refer to section 9.4 for details). As part of the initial consent to be contacted (Appendix 2), patients and delivery staff will be asked for their consent to be contacted by the process evaluation team. A subgroup of patients and delivery staff (including patients who agree to participate in the MOTION study and those who don't) will be asked to consent (using a separate process evaluation consent form and information sheet) to a brief interview by the process evaluation team to explore their decision making.

5.3 Withdrawal of participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form. The participant will have the option of withdrawal from all aspects of the trial but continued use of data collected up to that point. To safeguard rights, minimum personally identifiable information will be collected, and a withdrawal form completed. The trial management and trial steering committee will monitor these withdrawals from the trial. The process evaluation team will also be informed of any patient who previously gave permission for re-contact but has since withdrawn for the study.

6 STUDY ASSESSMENTS

Participant Follow-up at 12 and 24 months

All available methods of communication will be used for the study assessments including email, post, telephone and NHS approved video links (e.g. NearMe), with a maximum of two reminders sent where required. The preferred method for collection of baseline data will be with a face-face consultation. Where local circumstances prevent this, baseline data may also be collected by telephone or video link. After collection of the baseline data, follow up will occur at two further intervals - 12 and 24 months post-randomisation, with all study assessments at these time points undertaken remotely via email, post or telephone.

Minimum requirements/acceptable variations (MRAV) proforma

A standardised minimum requirements/acceptable variations (MRAV) proforma will be completed for each participant approximately 6 months post intervention to record the fidelity of the trial interventions. This proforma will be completed by the local research team at each participating centre. It should be noted that this proforma is collected from approximately 6 months post-intervention, and this interval may be different from the time period since randomisation due to NHS waiting lists. In the Personalises Knee Therapy (PKT) group, data will be collected and recorded at each one-to-one session. The date of the last one-to-one physiotherapy session (usually the 6th session) will be considered as the date for completion of the intervention.

	Table 2: Tabulated summary of assessments					
ASSESSMENT	**Screening**	**Baseline**	**6-month MRAV proforma (HTO)**	**6-month MRAV proforma (PKT)**	**12-month PROMS**	**24-month PROMS**
Who is responsible for assessment?	Local site team	Local site team	Local site team	Local site team	ECTU	ECTU
Allowed variation in months			±6	±6	±3	±3
How is assessment done?	Clinic review *and/or* Medical records review	Clinic review	Medical records review	Patient attendance at 6 supervised physiotherapy sessions Medical records review Patient exercise diary review	Email *and/or* Post *and /or* Online portal	Email *and/or* Post *and /or* Online portal
Assessment of eligibility criterion	X	X				
Log of eligible patients excluded (declined, exclusion criterion, other reason)		X				
Written Informed consent		X				
Baseline data & demographics		X				
Randomisation		X				
Minimum requirement/acceptable variation (MRAV) proforma			X	X		
Primary outcome score – KOOS		X			X	X
Oxford Knee Score (OKS)		X			X	X
Forgotten Joint Score (FJS)		X			X	X

EuroQoL score (EQ-5D-5L)		X			X	X
Pittsburgh Sleep Problem Scale		X			X	X
Return to Work/Employment questionnaire		X			X	X
Additional operative intervention in study knee					X	X
Complications					X	X

(MRAV- minimum requirements/acceptable variations proforma; PROMS – Patient reported outcome measures; ECTU – Edinburgh Clinical Trials Unit)

7 DATA COLLECTION

The database and data management plan will be created, validated, and administered by the Edinburgh Clinical Trials Unit (ECTU), following Standard Operating Procedures. All data will be collected by those trained and delegated via the site delegation log. Follow ups at 12 and 24 month will be collected centrally by Edinburgh clinical Trials Unit (ECTU) via provision of an online portal or postal/emailed follow ups.

7.1 Source Data Documentation

The investigator will maintain source documents for each patient in the study (hospital or clinical medical records) containing demographic and medical information. All information relevant to a participant's general medical history on CRFs must be traceable to these source documents in the patient's case notes.

The study CRF's and patient questionnaires will be used as source data but data relevant to a participant's general medical history will be recorded also in the electronic case notes.

All source data documents are detailed separately to the protocol.

Case Report Forms

Electronic data collection will be set up by the ECTU using local software.

8 DATA MANAGEMENT

8.1 Personal Data

Patient details (including name, address, telephone number, email address, age, sex, CHI/NHS number, Body Mass Index, relevant medical/surgical history and treatments) will be collected as part of this trial and to facilitate the central follow-up and Process Evaluation (only applicable for those that consent for their details to be shared with the

Process Evaluation Team). Personal data will be stored by the research team on University of Edinburgh secure servers. Personal data will be stored for a minimum of 10 years after the study end date to permit data linkage.

8.2 Data Information Flow

No data will be sent outside the UK.

8.3 Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

8.4 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

8.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS, DATA ANALYSIS AND PROCESS EVALUATION

9.1 Sample size calculation

The minimally clinically important difference (MCID) for the primary outcome measure is 8-10 (see KOOS website www.koos.nu), so we have used a value of 9, the mid-point of this range. To account for 20% unidirectional crossover from the non-surgical arm to the surgical arm, we have used an MCID of 7.2. If the observed treatment effect was going to be 9, then the observed mean KOOS in one arm would have been x, and in the other arm it would have been x+9. If there is 20% cross-over in one direction, and you analyse by intention-to-treat, then the observed mean KOOS in one arm is now still x, and in the other arm it is now [0.8(x+9) + 0.2x] = x+7.2. We have assumed the standard deviation for the KOOS will be 15 (13,41,42,43,44,45). To account for and adjusting for baseline KOOS, we have assumed a correlation between baseline and follow up measurement of 0.25. This reduces the standard deviation to 13. Variance2=(1-rho2) variance1where variance1=152, and rho=0.5 (From pg54 Julious, Sample sizes for clinical trials).Therefore new SD=$\sqrt{}$(168.75) ≈13.The intracluster correlation coefficient of the KOOS amongst surgeons is likely to be around 0.056 (60). Using this value, and assuming there will be approximately 5 patients per surgeon, gives a design effect of 1.224. [design effect = 1+(0.056*(5-1)) = 1.224]. We have adjusted for clustering among surgeons through multiplying by the square root of the design effect (1.106) to obtain a standard deviation in the surgical arm of 14.4. In the non-surgical intervention arm of the trial, the number and variety of physiotherapists treating each patient is variable, and clustering by physiotherapist is not appropriate.

However, the components of the non-surgical intervention are likely to be similar with each centre, and vary between centres, so clustering on centre within the non-surgical intervention arm is more appropriate. We have assuming that the intracluster correlation coefficient of the KOOS in the non-surgical intervention arm of each centre is 0.056. If there are 10 patients per centre, we get a design effect of 1.504. [design effect = 1+(0.056*(10-1)) = 1.504]. We have adjusted for clustering in the physiotherapy arm through multiplying by the square root of the design effect (1.226) to obtain a standard deviation in the physiotherapy arm of 15.9. Using 90% power, 2-sided p=0.05, with a difference of 7.2, and standard deviations of 14.4 and 15.9, this gives a sample size of 95 per group. Allowing for 15% loss to follow up gives112 per group.

9.2 Proposed statistical analyses

Our primary analysis will compare the KOOS at the 24-month follow-up, between the randomised treatment arms, using a linear mixed model adjusting for surgeon as a random effect. Clustering in the surgical and non-surgical arms will be considered according to the recommended method (51) and as detailed in the samples size calculation. There are no pre-planned subgroup analyses, and no pre-planned formal interim analyses. Analysis of secondary outcomes will follow similar methods to those proposed for the primary analysis, where the data are of an appropriate form. Full details will be held in a separate detailed statistical analysis plan, and will be finalised prior to the database being locked at the end of follow up for final analysis. We are expecting a very low amount of missing data for the scales (~10% of our primary outcome) and will perform a complete case analysis. Our primary analysis will be based on intention-to-treat, but a complier average causal effect (CACE) analysis will also be performed as a sensitivity analysis. The statistical aspects of this trial will follow the Standard Operating Procedures of ECTU.

9.3 Health economic analyses

Health economic analysis will include two components:

1. A within trial analysis will profile the short-term patterns of health and social care resource utilisation and health impacts over the observable 24-month trial period, and examine relative short term cost-efficiency of each trial.
2. A long run cost-efficiency model, extrapolating changes patient outcomes over a lifetime horizon to account for future impacts on the need for TKR and associated revision, and their timing relative to retirement.

Full details of these analyses will be specified in a comprehensive Health Economic Analysis Plan, authored by the study health economist(s), and signed off by the PI prior to analysis, however the following section offers an overview:

To maximise UK policy relevance, health economic analysis will follow NICE reference case recommendations (53) including: The adoption of an NHS and PSS (personal social service) costing perspective for primary analyses; cost-utility approach (results presented in terms of incremental cost effectiveness ratios (ICERs) on a cost per quality adjusted life year (QALY) basis, with QALYs derived from EQ-5D-5L utility scores using NICE`s preferred scoring algorithm at time of analysis); choice of discount rate (where applicable); and use of probabilistic sensitivity analysis (PSA). Secondary analysis will investigate the impact of treatment choice on employment status.

Several key items of health care resource utilisation (HCRU) for the first 24 months post randomisation will be collected retrospectively from medical records, namely: Inpatient admissions; A&E visits; ambulance trips; physiotherapy, and other outpatient visits. Additional top up self-report surveying will be undertaken alongside EQ-5D-5L and other PROMs at 12 and 24 months for: primary care, pain medications; employment status; and any HCRU not obtainable from medical records. HCRU will be combined with standard UK price weights (54) to estimate costs with a base year set to the latest financial year for which at least one study participant provides data.

The within trial analysis (component 1) will describe rates of resource use, associated cost, and health utility scores/QALYs, will be presented contextually as summary statistics for each trial arm, with comparisons of total cost and QALYs undertaken Generalised Linear Modelling to account for anticipated skew (55) Incremental cost per QALY will be estimated by appropriate technique with preference given a recycled predictions approach (56) if data permits. The proportion of patients changing employment status will be examined using logistic regression.

Missing data will be imputed using appropriate techniques depending on degree of missingness, most likely multiple imputation by chained equations (which is considered gold standard in this area (57). It is however worth noting that the most important cost factors relate to inpatient readmission and outpatient activity, will be obtained from medical records thus are not anticipated be prone to missingness.

Longer run cost-efficiency in terms of incremental cost per QALY will be examined by means of decision analytic simulation modelling (Component 2), This will extrapolate patient outcomes over a lifetime horizon to account for future impacts on the need for TKR and associated revision, and their timing relative to retirement since these often have significant impacts on employment potential and related. Initial scoping suggests this to be at least achievable Markov modelling, though as available data appear to be rich, more sophisticated options will be explored as needed. Initially reporting from the model will utilise the 24-month trial data, complimented with NJR and KOR data on longer term rates of TKR, revision TKR, and associated EQ-5D utility scores, a recent Cochrane review (12), topped up to date of analysis, and parameters extracted from a similar model (58). Additional, potentially non-systematic, targeted literature searches may be necessary for specific parameters if not available from these sources.

Uncertainty around both within trial and modelled ICERs will be presented using PSA with cost-effectiveness acceptability curves (CEAC) generated. Should the model prove inconclusive, value of information analysis will be undertaken to identify critical parameters which are driving overall uncertainty in decision criteria to inform follow up research potentially using the data linkage permissions obtained at consent.

9.4 Process Evaluation

In line with MRC guidance (52) a mixed method process evaluation will be conducted. The overall aim is to assess the acceptability and feasibly of the intervention from staff and patients. Specifically, it will address the following research objectives: (a) explore trial eligibility, recruitment and retention rates (b) acceptability of intervention implementation including trial processes and the collection of routine monitoring data (c) patient experience of taking part and the contextual factors that influence this.

A. Process evaluation design and sample: The design will comprise of two parts. Part 1 will be embedded within the pilot study, providing delivery detail and context to

support the main trial. Data will be collected, via semi-structured telephone/video interviews from delivery staff (n=12, surgeons/physiotherapists/research nurses) at three sites and patients enrolled in the pilot stage (n=15- 20, minimum of four from each site and minimum of four from the control arm) to capture initial understanding/expectations of the trial. They will then be followed up once (via semi-structured telephone interview) during the pilot study (months 3-6). Staff interviews will explore experiences of taking part, challenges to recruitment/implementation and issues related to trial delivery. Patient interviews will explore willingness to be randomised and acceptability of intervention or the non-surgical package if in comparison group. Findings will be fed back to the Trial Management Group and Trial Steering Committee to improve recruitment/trial delivery for the definitive trial. Part 2 will extend the process evaluation into the definitive trial. This is important because the pilot trial data captures just one follow-up from three sites, providing limited detail on the research objectives listed above and the factors that influence this. By extending the process evaluation into the definitive trial, the design will move to a prospective, longitudinal, cohort study across six sites. The total sample will be boosted to 20 staff and 30-40 patients (~7-10 control and ~23-30 intervention, spread across the three sites). This will further our understanding of the trial implementation, context (delivery may vary by site, for example) and the mechanisms that influence delivery. It will also provide a richer narrative of the patient journey and stakeholder views, which will inform future roll out and create transferable learning to other disciplines. For example, a key area is to explore movement from the non-surgical to surgical arm of the trial. Being able to examine this over multiple time periods will generate a greater depth of understanding of the context in which this occurs and the factors that influence the patient decision to switch. Patients will receive three further telephone interviews. The first at six months and then at 12 and 24 months in line with the clinical follow up. To prevent sample attrition, patients will receive £15 for each completed interview. Finally, it is important to understand the reasons why potentially eligible patients decided not to take part in the trial and if there is anything that could have been done differently to encourage participation in the future. We will, therefore, conduct 10 telephone interviews with these patients, who will also be given a £25 voucher.

B. Recruitment and analysis: Recruitment of patients will be guided by a purposive sampling frame to ensure diversity of key characteristics e.g. trial site, treatment arm, age, gender, urban rural residence. Interviews will be digitally recorded and transcribed verbatim by an in house employee of the University of Edinburgh. Audio files will be saved within the secure project folder prior to being downloaded for transcription. Once the transcript is checked, the audio file will be deleted.

We will use a thematic approach to analyse the data, facilitated by NVivo 12. First, we will read the transcripts to identify the key topics and issues which emerge from data. Next, a draft analytical framework will be created, piloted, refined and finalised by the project team. Each transcript will then be coded and summarised into key themes using Framework matrices, or charts. This approach reduces large volumes of data and facilitates systematic between and within case analysis. It also allows for emergent patterns and explanations to be explored and tested and, thus, provides the depth required to move beyond description and into interpretative analysis, which is the aim of qualitative analysis. The use of NVivo 12 ensures that analysis is fully documented and conclusions can be clearly linked back to the original source data.

10 ADVERSE EVENTS

Adverse events will be collected throughout the trial. Events related to a worsening of co-morbid conditions known at time of randomisation and any events related to the known risk associated with surgery will not be reported as adverse events. Complications already covered under secondary outcomes (Protocol Section 2.2) will not be recorded as adverse outcomes. Adverse events will be collected for all patients up to their final (24-month) follow up. These do not require to be reported to the Sponsor.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency. Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

he Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose

of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

12.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.4 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach

on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 10 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.7 END OF STUDY

The end of study is defined as the last participant's last visit/last follow-up.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

No interventions will be provided past the end of the trial unless agreed locally at site.

12.9 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study resides with the study team.

14 REFERENCES (as listed in approved MOTION Detailed Research Plan)

1. Brouwer RW et al. Osteotomy for treating knee osteoarthritis. Cochrane Database Syst Rev. 2014;12:CD004019. Epub 2014 Dec 13
2. Niinimäki TT et al. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: Finnish registry-based study of 3195 knees. JBJS-B 2012;94(11):1517-21
3. Arthritis Research UK (2013). Osteoarthritis in General Practice. www.versusarthritis.org
4. Osteoarthritis: Care and Management in adults. NICE Clinical Guideline CG177. February 2014
5. Jordan K et al. A prospective study of the consulting behaviour of older people with knee pain. British Journal of General Practice. 2006; 56(525):269-276
6. Sanders C et al. Unmet need for joint replacement: a qualitative investigation of barriers to treatment among individuals with severe pain and disability of the hip and knee. Rheumatology 2004; 43(3):353-357
7. National Joint Registry (NJR). www.njrcentre.org.uk.15th Annual report 2018.
8. Scott CEH et al. Predicting dissatisfaction following TKA in patients under 55 years of age. BJJ 2018:98(12);1625-1634
9. Scott CEH et al. Activity levels and return to work following total knee arthroplasty in patients under the age of 65. BJJ 2017: 99-B(8); 1037-1046
10. Scott CEH et al. Activity levels and return to work after revision total hip and knee arthroplasty in patients under 65 years of age. BJJ 2018: 100-B(8)
11. Bayliss LE et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. The Lancet. 2017;389(10077):1424-30
12. Smith WB et al. Medial compartment knee osteoarthritis: age-stratified cost-effectiveness of total knee arthroplasty, unicompartmental knee arthroplasty, and high tibial osteotomy. KSSTA 2017: 25(3);924-933
13. Emery CA et al. Establishing outcome measures in early knee osteoarthritis. Nat Rev Rheumatol. Nature Publishing Group; 2019 Jun 14;15(7):438–48
14. Beard DJ et al.. The clinical and cost-effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial. The Lancet. 2019;394:746-56
15. Willis-Owen CA et al. Unicondylar knee arthroplasty in the UK National Health Service: an analysis of candidacy, outcome and cost efficacy. The Knee. 2009 Dec 1;16(6):473-8
16. Hoorntje A et al. High Rates of Return to Sports Activities and Work After Osteotomies Around the Knee: A Systematic Review and Meta-Analysis. Sports Med 2017;47(11);2219-2244
17. McCulloch P et al. Surgical Innovation and Evaluation 3 No surgical innovation without evaluation: the IDEAL recommendations. The Lancet. Elsevier Ltd; 2009 Sep 26;374(9695):1105–12
18. Seil R et al. The rapid evolution of knee osteotomies. Knee Surg Sports Traumatol Arthrosc. 2012 Aug 10;21(1):1–2
19. Smith JO et al. Osteotomy around the knee: evolution, principles and results. Knee Surg Sports Traumatol Arthrosc. 2012 Sep 29;21(1):3–22

20. El-Galaly A et al. Prior High Tibial Osteotomy Does Not Affect the Survival of Total Knee Arthroplasties: Results From the Danish Knee Arthroplasty Registry. J Arthroplasty 2018; 33(7); 2131-2135
21. UK Knee Osteotomy Registry (UKKOR). www.ukkor.co.uk. First report of the UK Knee Osteotomy Registry (UKKOR) 2018.
22. Ollivier B et al. Good long-term survival and patient-reported outcomes after high tibial osteotomy for medial compartment osteoarthritis [published online ahead of print, 2020 Sep 9]. Knee Surg Sports Traumatol Arthrosc. 2020;10.1007
23. Fransen M et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49(24):1554-7
24. Fernandes L et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72:1125-35
25. McAlindon TE et al. OARSI guidelines for the non- surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22: 363-88
26. Nelson AE. A systematic review of recommendations and guidelines for the management of osteoarthritis: the Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. Semin Arthritis Rheum 2014;43:701
27. Deyle GD et al. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. New England Journal of Medicine. 2020 Apr 9;382(15):1420-9
28. Skou ST et al. The efficacy of 12 weeks non-surgical treatment for patients not eligible for total knee replacement: a randomized controlled trial with 1-year follow-up. Osteoarthritis Cartilage. 2015;23(9):1465-75
29. Skout ST et al. Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from two parallel randomized controlled trials. Osteoarthritis Cartilage. 2018;26(9):1170-1180
30. Skou ST et al. A 12-week supervised exercise therapy program for young adults with a meniscal tear: Program development and feasibility study.Mov Ther. 2018;22(3):786-791
31. Hamilton DH et al. Worsening adherence to OARSI guidelines for the non-operative management of hip and knee osteoarthritis. Proceedings of the Osteoarthritis, Research Society International, 2018, Liverpool
32. Simpson AHRW, Hamilton DF et al. Targeted Rehabilitation to Improve Outcome after total knee replacement (TRIO): study protocol for a randomised controlled trial. Trials. 2014;15:44 DOI: 10.1186/1745-6215-15-44
33. Woolf AD et al. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646-56
34. www.jla.nihr.ac.uk/priority-setting-partnerships/early-hip-and-knee-osteoarthritis/top-10-priorities.htm
35. Simpson AH et al. Orthotics, Rehabilitation, Topical and oral agent Usage and Nutrition to Improve ouTcomes at 1 Year (OPPORTUNITY): study protocol for a randomised controlled trial. *Trials* 2020;21:209
36. Wall PD et al. Personalised Hip Therapy: development of a non-operative protocol to treat femoroacetabular impingement syndrome in the FASHIoN randomised controlled trial. BJSM. 2016; 50(19):1217-23
37. Skou ST et al. N Engl J Med. A Randomized, Controlled Trial of Total Knee Replacement. 2015 Oct 22;373(17):1597-606
38. Damian R Griffin et al. FASHIoN Study Group. Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. Lancet. 2018 Jun 2; 391(10136): 2225–2235

39. Antony J R Palmer et al. Arthroscopic hip surgery compared with physiotherapy and activity modification for the treatment of symptomatic femoroacetabular impingement: multicentre randomised controlled trial BMJ. 2019; 364: l185
40. Palmer JS et al. Surgical interventions for symptomatic mild to moderate knee osteoarthritis. Cochrane Database of Systematic Reviews. 2019(7)
41. Roos EM et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self- administered outcome measure. Journal of Orthopaedic & Sports Physical Therapy. 1998;28(2):88-96
42. Collins N. et al. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta- analysis of measurement properties. Osteoarthritis Cartilage 2016. 24, 1317–1329
43. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003 Nov 3;1:64
44. Clement ND et al. What is the Minimum Clinically Important Difference for the WOMAC Index After TKA? Clin Orthop Relat Res. 2018 Oct;476(10):2005–14
45. www.koos.nu (website for primary ourcome score)
46. Harris, KK et al. Extending the use of PROMs in the NHS—using the Oxford Knee Score in patients undergoing non-operative management for knee osteoarthritis: a validation study.*BMJ open* 3.8 (2013): e003365
47. Giesinger JM et al. Development of a computer-adaptive version of the forgotten joint score. J Arthroplasty. 2013;28(3):418–422
48. www.forgotten-joint-score.info
49. EQ-5D-5L – EQ-5D (euroqol.org)
50. Jenkins CD et al. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol1988;41:313–21
51. Flight L et al. Recommendations for the analysis of individually randomised controlled trials with clustering in one arm–a case of continuous outcomes. BMC Medical Research Methodology. 2016;16(1):165
52. Moore GF et al. Process evaluation of complex interventions: Medical Research Council guidance. bmj, 2015. 350: p. h1258
53. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013, London: NICE Publications 2013
54. Curtis L. Unit Costs of Health & Social Care 2016.Kent: Personal Social Services Research Unit 2019. Department of Health, The Reference Costs Publications. The Department of Health 2019. https://www.gov.uk/government/collections/nhs-reference-costs
55. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ 2001;20:461-94
56. Glick HA et al. Economic Evaluation in Clinical Trials. Oxford: Oxford University Press 2007
57. White IR et al. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2010;30:377-399
58. Briggs A et al. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006
59. Costa ML et al. Do large pragmatic randomised trials change clinical practice?: assessing the impact of the Distal Radius Acute Fracture Fixation Trial (DRAFFT). Bone Joint J 2016;98-B:410-3.
60. Cook JA et al. Clustering in surgical trials - database of intracluster correlations. Trials 2012;13:2

61. Snow M, Jermain P, Mandalia V, Murray J, Khakha R, McNicholas M, Dawson M. A 2021 consensus statement on osteotomies around the knee by the UK Knee Osteotomy consensus Group (KOG). The Knee. 2021 Dec 1;33:73-83.
62. Rolfson O, Wissig S, van Maasakkers L, Stowell C, Ackerman I, Ayers D, Barber T, Benzakour T, Bozic K, Budhiparama N, Caillouette J. Defining an international standard set of outcome measures for patients with hip or knee osteoarthritis: consensus of the international consortium for health outcomes measurement hip and knee osteoarthritis working group. Arthritis care & research. 2016 Nov;68(11):1631-9.

15 APPENDIX

Appendix 1 – MOTION PISCF

Appendix 2 – MOTION Consent to contact form