HIPSTER PROTOCOL

HIP Surgical Techniques to Enhance Rehabilitation (HIPSTER) – A randomised controlled trial

IRAS number	327702
ISRCTN number	27974201
Sponsor	Royal Devon University Healthcare NHS Foundation Trust
Funding number	NIHR150537
Funding body	MRC and NIHR Efficacy and Mechanism Evaluation programme
Ethics approval date	19/09/2023
Version number	7.0
Date	31/03/2025
Stage	Final

This protocol has regard for the HRA guidance and order of content.

PROTOCOL AMENDMENTS

Amendment no.	Protocol version no.	Date of approval	Author(s) of changes	Details of changes made
SA001	5.0	06/02/2024	Holly Whitmore	Reference to documenting any additional surgical procedures at the 6 month (26 weeks) and 12 month (52 weeks) follow-up time points. Amended sections: 6.7.1, 6.7.7 and 6.7.8.
NSA002	6.0	09/09/2024	Holly Whitmore	Key contacts section: updated title for Co-CI. Reference to collecting ethnicity data at screening and baseline

				time points. Amended sections: 6.2, 6.7.1 and 6.7.3. Reference to collecting comorbidity data at baseline time point. Amended sections: 6.7.1 and 6.7.3. Reference to options of reconfirmation of participation. Amended section: 6.3 Addition of expected reportable AE; haematoma. Section 7.2.3. Replacing “consent” with “initial screening” with reference to participant flow through trial in section 8.3.
SA002	7.0		Holly Whitmore Fiona Warren	Increasing the sample size by 30 participants. Amended sections: Trial Summary, 8.1 and 8.2.

KEY TRIAL CONTACTS

Chief Investigator (CI)	Mr Al-Amin Kassam Royal Devon University Healthcare NHS Foundation Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 262173 al-amin.kassam@nhs.net
Co-Chief Investigator (Co-CI)	Prof Timothy Holsgrove Department of Engineering Harrison Building North Park Road Streatham Campus University of Exeter Exeter EX4 4QF +44 (0)1392 724682 t.holsgrove@exeter.ac.uk
Sponsor	Dr Alison Kerridge Royal Devon University Healthcare NHS Foundation Trust Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 403041 alison.kerridge@nhs.net
Funder	National Institute for Health and Care Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS 02380 591661 monitoring@nihr.ac.uk
Trial Manager	Mrs Holly Whitmore Royal Devon University Healthcare NHS Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 403473 holly.whitmore@nhs.net
Co-Investigator	Mr Andrew Timperley Royal Devon University Healthcare NHS Foundation Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 262173 john.timperley@nhs.net

Co-Investigator	Ms Alison Smeatham Royal Devon University Healthcare NHS Foundation Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 262173 alison.smeatham@nhs.net
Co-Investigator	Mrs Lizzy Gordon Royal Devon University Healthcare NHS Foundation Trust Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 403041 elizabeth.gordon2@nhs.net
Co-Investigator and Statistician	Dr Sarah Whitehouse Royal Devon University Healthcare NHS Foundation Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 262173 sarah.whitehouse7@nhs.net
Co-Investigator and Director of Exeter Clinical Trials Unit	Prof Siobhan Creanor Exeter Clinical Trials Unit College House University of Exeter St Luke's Campus Heavitree Road Exeter EX1 2LU +44 (0)1392 722700 E.S.Creanor@exeter.ac.uk
Co-Investigator and Senior Trial Statistician	Dr Fiona Warren Exeter Clinical Trials Unit College House University of Exeter St Luke's Campus Heavitree Road Exeter EX1 2LU +44 (0)1392 722749 F.C.Warren@exeter.ac.uk
Data Management and Project Management Support	Exeter Clinical Trials Unit College House University of Exeter St Luke's Campus Heavitree Road Exeter EX1 2LU +44 (0)1392 722700 ctu@exeter.ac.uk

GENERAL ENQUIRIES

For general queries and trial information please contact:

Trial Manager	Mrs Holly Whitmore Royal Devon University Healthcare NHS Foundation Trust Princess Elizabeth Orthopaedic Centre Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter EX2 5DW +44 (0)1392 403473 HIPSTER@exeter.ac.uk

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CAPA	Corrective And Preventative Action plan
CI	Chief Investigator
Co-CI	Co-Chief Investigator
Co-I	Co-Investigator
CK	Creatine Kinase
CRC	Clinical Research Collaboration
CRF	Case Report Forms
CRP	C-Reactive Protein
CT	Computerised Tomography
CTU	Clinical Trials Unit
DAA	Direct Anterior Approach
DMC	Data Monitoring Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EME	Efficacy and Mechanism Evaluation
ExeCTU	Exeter Clinical Trials Unit
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trial Number
LEFS	Lower Extremity Functional Scale
MCID	Minimal Clinically Important Difference
MDT	Multidisciplinary Team
MHRA	Medicines Healthcare Products Regulatory Agency
MIC	Minimal Important Change
MID	Minimal Important Difference
NIHR	National Institute of Health Research
NHS	National Health Service
NJR	National Joint Registry of England, Wales, Northern Ireland, and the Isle of Man
OACS	Oxford Arthroplasty Early Change Score
OARS	Oxford Arthroplasty Recovery Score
OECD	Organisation for Economic Co-operation and Development

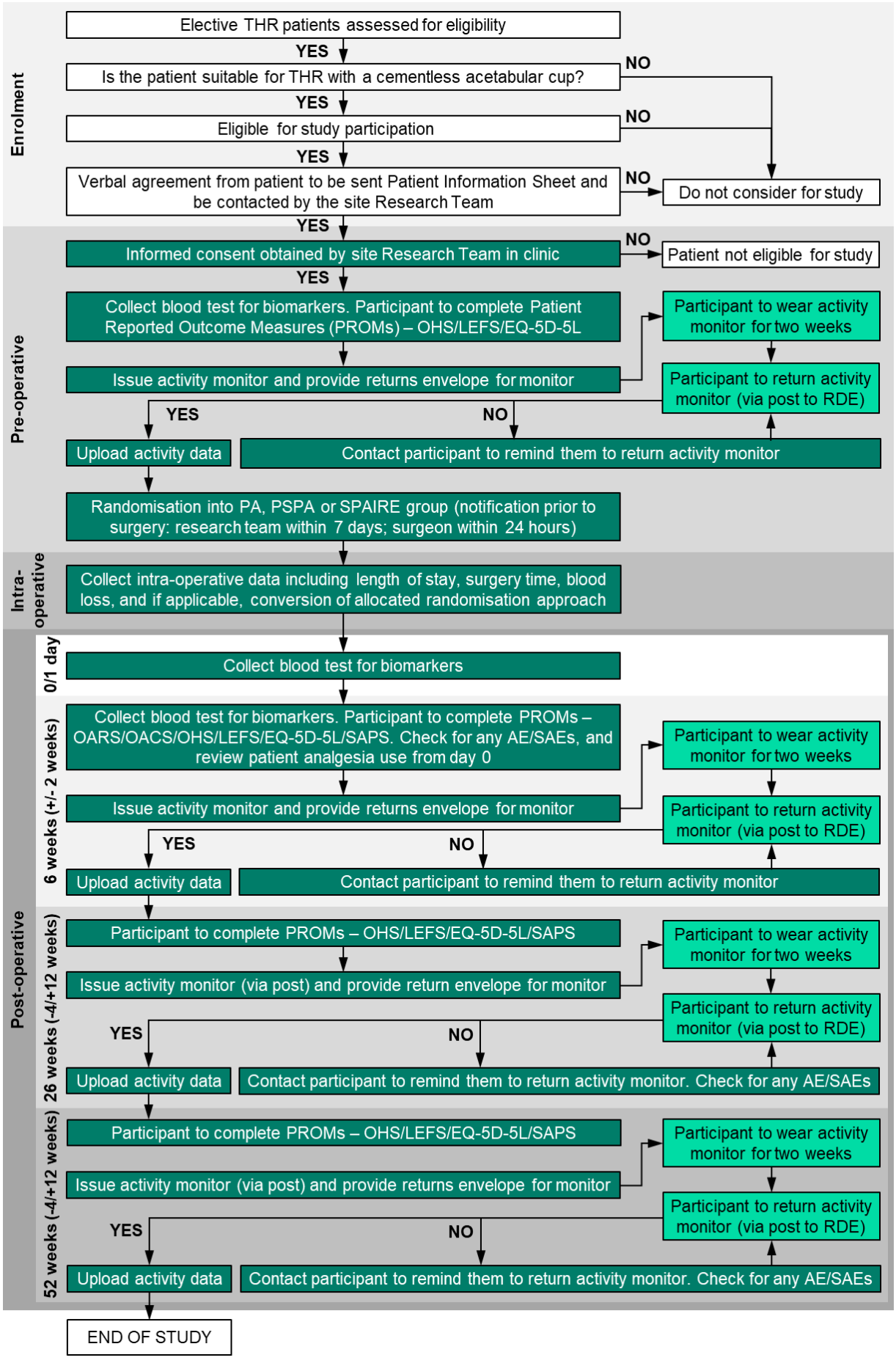
OHS	Oxford Hip Score
PA	Posterior Approach
PI	Principal Investigator
PPIE	Patient and Public Involvement and Engagement
PROMs	Patient Reported Outcome Measures
PSPA	Piriformis Sparing Posterior Approach
QMS	Quality Management System
RC	Research Coordinator
RCT	Randomised Controlled Trial
RDE	Royal Devon & Exeter (Wonford) Hospital
RDUH	Royal Devon & Exeter University Healthcare NHS Foundation Trust
REC	Research Ethics Committee
RUSAE	Related and Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAPS	Self-Administered Patient Satisfaction Scale
SD	Standard Deviation
SER	Short External Rotators
SHR	Swedish Hip Register
SOP	Standard Operating Procedure
SPAIRE	Spare Piriformis And Internus Repair Externus
THR	Total Hip Replacement
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoE	University of Exeter
WHO	World Health Organisation

TRIAL SUMMARY

Trial title	Hip Surgical Techniques to Enhance Rehabilitation
Short title	HIPSTER
Clinical phase	III
Trial design	Single-centre, double-blind, parallel three-arm, randomised-controlled, superiority trial
Trial participants	People undergoing an elective total hip replacement (THR)
Planned sample size	339 (originally 309; amended following DMC recommendation and TSC endorsement)
Follow-up duration	Primary endpoint: 6 weeks post-op Secondary endpoints: day 0/1 post-op, 6 weeks post-op, 6 months (26 weeks) post-op, 12 months (52 weeks) post-op
Planned trial period	From 01/01/2023 to 31/12/2026
Source of Funding	National Institute of Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme: NIHR150537
Primary objectives	To evaluate whether either of two novel, tendon-sparing approaches to THR, the piriformis-sparing posterior approach (PSPA) and the spare piriformis and internus repair externus approach (SPAIRE), provide any benefits to patients compared to the current standard posterior approach (PA) using the Oxford Arthroplasty Recovery Score (OARS) patient reported outcome measure (PROM) 6 weeks after surgery.
Secondary objectives	To compare differences between SPAIRE, PSPA, and PA in terms of muscle damage and global inflammation using serum creatine kinase (CK), and C-reactive protein (CRP) blood biomarkers pre-operatively and post-operatively at day 0/1 and 6 weeks. To compare differences between SPAIRE, PSPA, and PA in terms of length of hospital stay, duration of surgery, and blood loss. To investigate potential mechanisms of action of the three forms of surgery in terms of their effect on OARS, using mediation analysis with CK and CRP as mediators of OARS. To compare differences between SPAIRE, PSPA, and PA in terms of participant walking (daily steps, step rate, and walking bout time), and sleep parameters (daily sleep time, and sleep quality) measured via an activity monitor worn for 2 weeks at pre-operative assessment, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks). To compare differences between SPAIRE, PSPA, and PA in terms of PROMs (Oxford Hip Score, Lower Extremity Function Scale, EuroQol 5D-5L, and Self-Administered Patient Satisfaction) pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks).

	To compare differences between SPAIRE, PSPA, and PA in terms of additional analgesic use from immediately post-surgery up to 6-weeks post-operatively. To use the post-operative follow-ups at 6 weeks, 6 months (26 weeks) and 12 months (52 weeks) to compare the trajectory of outcome measures between the three groups and evaluate whether there are any differences in outcomes over time across the groups. To evaluate safety of PSPA and SPAIRE, by reporting related adverse events and serious adverse events.

TRIAL FLOWCHART



FUNDING AND SUPPORT IN KIND

FUNDER	FINANCIAL SUPPORT GIVEN
NIHR Efficacy and Mechanism Evaluation (EME)	£916,086.21 £942,352.21 (including NHS Support Costs)

ROLE OF THE TRIAL SPONSOR, FUNDER, AND CLINICAL TRIALS UNIT

Royal Devon University Healthcare NHS Foundation Trust is the named Sponsor for this trial, and will be supported by the UKCRC fully registered, and British Orthopaedic Association- affiliated, Exeter Clinical Trials Unit (ExeCTU) and the Department of Engineering at the University of Exeter. The Sponsor has had input into the design of the trial but overall responsibility for the design lies with the Chief Investigator (CI) and Co-Chief Investigator (Co-CI). The Sponsor is responsible for authorising the initial submission to the Research Ethics Committee (REC) and Health Research Authority (HRA) and subsequent amendments, ensuring appropriate agreements and indemnity arrangements are in place, overseeing the conduct of the trial and ensuring it adheres to the relevant principles of good clinical practice (GCP) and the UK Policy Framework for Health and Social Care Research, and for archiving at the end of the trial. The Sponsor is not responsible for and has no involvement in the data analysis or interpretation, or writing manuscripts.

The NIHR as funder is responsible for providing funds to cover the agreed research costs. The funder is not responsible for and has no involvement in data analysis or interpretation, or writing manuscripts. ExeCTU, University of Exeter, provides project oversight, support and mentorship of the Trial Manager, database development and data management, and statistical analyses. Responsibilities of ExeCTU, the Sponsor, CI, and Co-CI are defined in detail in a separate task allocation matrix. ExeCTU will be closed on bank holidays and University of Exeter (UoE) closure days; only emergency trial support will be available at these times.

ROLES AND RESPONSIBILITIES OF THE TRIAL MANAGEMENT AND TRIAL OVERSIGHT COMMITTEES AND INDIVIDUALS

Trial Management Group

The Trial Management Group (TMG) will be composed of the CI and Co-CI, Trial Co-Applicants, Trial Statisticians, Patient and Public Involvement and Engagement (PPIE) lead with at least one lay representative, the Trial Managers, and a Sponsor's representative. The TMG will write the protocol, Statistical Analysis Plan (SAP) and participant-facing materials, obtain relevant approvals from an NHS REC and the Health Research Authority (HRA), and ensure the trial is conducted according to the relevant principles of GCP and the UK Policy Framework for Health and Social Care. The TMG will meet monthly for the first 18 months of the trial, then at least every three months thereafter to manage the day-to-day running of the trial, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the TMG will analyse the data, interpret the analyses, write reports to the Funder, and write and submit manuscripts to peer-reviewed journals.

Trial Steering Committee

The Trial Steering Committee (TSC) will be composed of an independent Chairperson with expert knowledge in the subject area, an independent Statistician, PPIE representative and at least one other independent professional member. The CI, Co-CI, and Senior Trial Statistician will join the TSC as observers and will not be voting members. The Trial Manager, Trial Statistician and representatives of the Sponsor and the Funder will be invited to attend TSC meetings also as

observers and will not be voting members. The role of the TSC is to monitor and supervise the progress of the trial. The TSC chair and/or TSC committee will review the final protocol prior to submission to REC/HRA and the independent statistician on the TSC will approve the statistical analysis plan prior to final database lock. The TSC will meet prior to recruitment commencing and at least six-monthly thereafter. Further details of the roles and responsibilities of the TSC are documented in the TSC charter, available upon request to the Trial Manager.

Data Monitoring Committee

The Data Monitoring Committee (DMC) will be composed of a minimum of three independent professional members, including a statistician. The CI and Co-CI, Senior Trial Statistician and Trial Manager will be invited to attend the open sessions of DMC meetings but will not be voting members. The Senior Trial Statistician will be unblinded throughout the trial and the Trial Statistician will remain blinded until completion of the primary analyses for the primary and secondary outcomes. Only the unblinded statistician(s) can be invited to the closed section of DMC meetings and will prepare/review unblinded sections of the DMC report. The DMC will monitor accumulating trial data, including safety, and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or early closure of the trial. The DMC will meet prior to recruitment commencing and at least 6-monthly thereafter. Further details of the roles and responsibilities of the DMC are documented in the DMC charter, available upon request to the Trial Manager.

Patient Advisory Group

An overarching Patient Advisory Group led by the PPIE lead will review patient-facing materials prior to ethical review and will have input into any revisions to patient-facing materials throughout the trial. This group will meet once a year.

The Site Research Team

The site Research Team will be responsible for the delivery of trial activities on site. This team consists of Research Nurses, Research Practitioners and a Senior Trials Administrator. The site Research Team is led by the Team Lead and will work closely with the Trial Manager/Research Co-ordinator and clinicians.

KEYWORDS

Total hip replacement; total hip arthroplasty; posterior approach; piriformis sparing posterior approach; spare piriformis and internus repair externus; double-blind, parallel three-arm, randomised-controlled, superiority trial

1 BACKGROUND AND RATIONALE

Musculoskeletal disorders are the leading global cause of years lived with disability [1]. Osteoarthritis is a key contributor to this, and 8% of the UK population over the age of 45 (2.1 million people) have sought treatment for osteoarthritis of the hip [2]. Total Hip Replacement (THR) surgery can be used to replace both the ball (femoral head) and socket (acetabular) parts of the hip with artificial components to restore the joint, with the aim of providing relief from pain and improving mobility.

THR is a highly successful surgical procedure, with over 100,000 THRs performed annually in the United Kingdom (UK). The National Joint Registry of England, Wales, Northern Ireland, and the Isle of Man (NJR), and the Swedish Hip Register (SHR) report similar 10-year survivorship of primary THR implants of approximately 95% [3, 4]. However, patient-reported outcome measures (PROMs) show that 12 months (52 weeks) after THR surgery, a substantial proportion of patients (12.3%) report moderate to severe pain in the operated hip, 7.4% of patients have severe problems or are unable to complete their usual daily activities, and 6.3% are dissatisfied or very dissatisfied with their operation [4]. Furthermore, all these outcomes worsen by the time of 5-year and 10-year follow-up [4]. These results demonstrate that whilst clinical outcomes such as survivorship of the implant are extremely good for THR, there remain significant challenges to overcome in terms of post-surgical pain, activity, and patient satisfaction.

There are several surgical approaches that can be used for THR, but the posterior approach (PA) is used in 54-66% of primary THR procedures in the UK, Sweden, New Zealand, and the United States [4-7], and is estimated to be the most commonly used approach worldwide [6, 8-11].

The PA (Figure 1a) involves cutting (releasing) and then repairing three musculo-tendinous structures (piriformis, obturator internus, and obturator externus), which are part of a group of muscles known as the short external rotators (SERs). Releasing and repairing tendons during THR has been shown to lead to increased fatty infiltration in the muscle, and a reduction in muscle volume [11-13], which may have a detrimental effect on muscle function. At 3 months after THR using the PA, the operated side is significantly weaker than the contralateral side in hip external rotation (50%) and hip extension (26%) [14], and this weak external rotation is still present 12 months after surgery [15].

Tendons that are released and subsequently repaired have an increased risk of failure, with failure of tendon repair reported as high as 86% (43/50) in patients following arthroplasty [16].

Given these challenges, modified PAs have been developed to reduce musculo-tendinous damage during surgery to improve stability, proprioception, and rehabilitation. These include the piriformis sparing posterior approach (PSPA), and the spare piriformis and internus repair externus (SPAIRE) approach (Figure 1b and 1c). Evidence suggests that tendons released during THR, with subsequent repair, are at risk of fatty muscle atrophy, and the potential for increased pain and reduced function. These factors may be responsible for the cohort of patients who remain dissatisfied even after a technically well implanted THR.

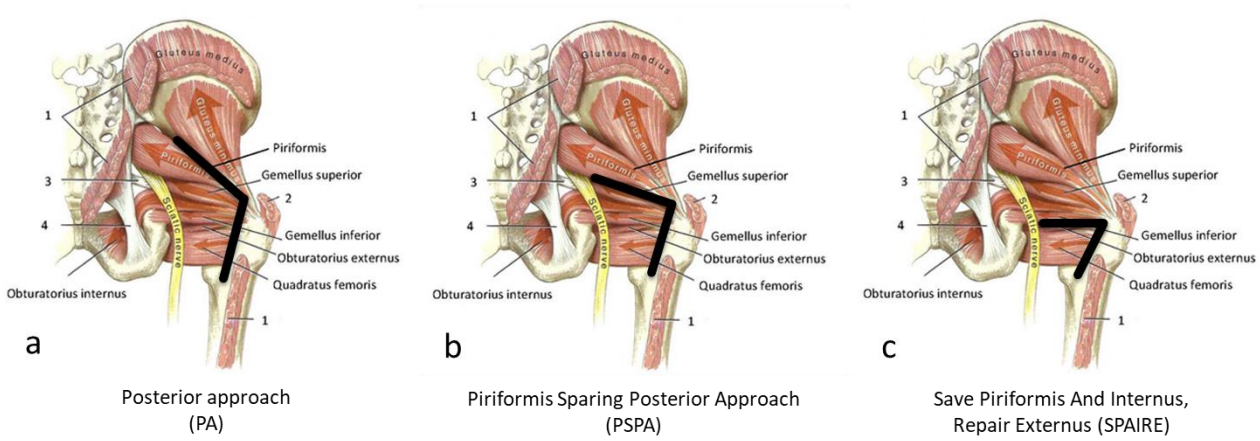


Figure 1: The three surgical approaches that will be investigated in the project, with the lines of dissection and tendon release denoted with thick black lines. PA releases three tendons (a), the PSPA releases two (b), and the SPAIRE approach releases only one tendon (c).

The PSPA (Figure 1b) involves the release of two tendons (obturator internus and obturator externus), preserving the piriformis tendon. MRI analysis has shown that the PSPA leads to higher quality piriformis muscle (lower fatty infiltration) 3 months and 2 years post-operatively compared to a standard PA [12]. Furthermore, this improved muscle quality in PSPA patients is combined with greater muscle volume 10 years post-operatively compared to PA patients, with a median percentage increase in muscle bulk of 19% in PSPA patients, and a median percentage decrease of 44% in PA patients [13].

These studies provide evidence that reducing the number of tendons that are released during THR can improve muscle quality and bulk, reduce pain, and accelerate post-operative recovery and rehabilitation. However, there remains a lack of high-quality, suitably powered, randomised studies to understand if these benefits of the PSPA, compared with the PA, translate to improved PROMs, improved post-operative activity levels, and increased patient satisfaction.

A further modification of the PA in which only one tendon is released, referred to as the SPAIRE approach (Figure 1c), has been developed by Professor Timperley and colleagues, and has been used in the clinical setting for THR since 2016 [17]. The SPAIRE approach has been adopted by multiple surgeons in the UK, and a retrospective cohort series using a procedure similar to the SPAIRE approach reported a reduced rate of dislocation compared to the PA [18]. SPAIRE further minimises soft tissue damage but is a more challenging procedure than the PSPA. Although the reduced number of tendons released using the SPAIRE approach may lead to improved hip stability, muscle function and proprioception, in addition to reduced pain and faster rehabilitation, the benefits of this approach currently remain theoretical.

The increased challenge of component positioning in tendon-sparing THR approaches such as the PSPA and SPAIRE approach can be negated with robotic guidance. Domb et al reported that the use of the MAKO Robotic Arm Assisted Surgery system (Stryker, Mahwah, New Jersey, USA) results in a significantly higher proportion of acetabular components correctly positioned in Lewinnek's safe zone (100%) compared with conventional THR (80%) using the PA [19]. A follow-up retrospective review trial of 1980 THR patients further demonstrated this, with a significantly higher proportion of acetabular components positioned in Lewinnek's safe zone using a robotic-assisted PA (98%) compared with non-assisted PA (70%) [20].

Current and previous relevant clinical trials were identified using the WHO International Clinical Trials Registry Platform Search Portal using search terms related to surgical approach and total hip replacement. This resulted in 60 trials investigating the effects of surgical approach or technique on the outcomes of total hip replacement, which were registered between 2005 and 2021. Only five of

these studies use tendon-sparing posterior approaches, three of which included assessment of the PSPA (ACTRN12609000961246, ACTRN12615000845538, and ACTRN12610000551099), the results of which are summarised above [12, 13, 21]. However, there has not previously been a sufficiently powered RCT designed or performed to identify if the PSPA leads to a benefit in important patient-reported outcome measures. The SPAIRE approach provides even greater theoretical advantage over the PA, but, although this approach is used clinically [17] potential benefits have not yet been assessed through an RCT. An early trial comparing the outcomes of the first 40 consecutive SPAIRE procedures with 80 previous consecutive PA procedures showed a statistically significant improvement in the Self-Administered Patient Satisfaction Score (SAPS [22]), improvement in leg length discrepancy, with no increase in complication rate or morbidity [23, 24]

Therefore, a trial is needed to assess the efficacy of tendon-sparing posterior approaches, whilst mitigating for the increased complexity of these more challenging procedures; this can be achieved through the adoption of robotic-assisted surgery.

Relevant ongoing NIHR-funded projects were identified through the NIHR Funding and Awards Search Website by viewing all awards under the musculoskeletal health category, and completing additional searches relating to hip replacement and robotic-assisted surgery. This resulted in five ongoing trials relevant to the present proposal.

Based on the limitations of the previous studies to identify clinically meaningful differences between THR approaches, evidence searches were completed using PubMed relating to surgical approaches in total hip replacement surgery, and functional, performance, and patient reported outcome measures used to assess differences between THR patient groups. These outcome measures were explored further by the Research Team and through a PPIE workshop, facilitated by the Public Involvement team of the South-West Research Design Service, to explore patient and carer experiences of THR. The PPIE group was introduced to the overall research objective: to understand whether tendon-sparing approaches might improve the patient experience of THR. Outcome measures, including PROMs, performance outcome measures, and functional outcome measures, were discussed to identify the most suitable primary and secondary endpoints with which to assess the efficacy of the PSPA and SPAIRE approach compared with the standard PA.

Based on the feedback from the PPIE group, several outcome measures were identified for potential inclusion, in addition to the outcome measures collected as part of routine care:

- Hip abduction strength
- Hip external rotation strength
- Walking step rate and bout length
- Sleep quality
- Lower extremity function scale PROM [25]

This PPIE workshop, combined with pilot studies and additional PPIE consultation, led to the identification of the Oxford Arthroplasty Recovery Score (OARS) PROM as a suitable primary outcome measure, and secondary outcome measures that will provide additional measures of efficacy of the PSPA and SPAIRE approach compared with the PA.

2 ASSESSMENT AND MANAGEMENT OF RISK

All three surgical approaches (PA, PSPA, and SPAIRE) are already being used in the clinical setting. However, the use of the SPAIRE approach for THR using robotic assistance is currently limited, and extending this trial to include other sites with a MAKO robot would require training for both the PSPA and SPAIRE approach. This would include the inherent learning curves associated with adopting new technology and surgical methods. Therefore, the trial will be restricted to a single centre of excellence, where the MAKO robotic-guidance system is used in routine THR surgery, and all the surgical procedures that will be used in this trial have also been performed in routine THR surgery, both without and with robotic guidance. As such, the trial is considered to pose a risk no greater than standard medical care in this setting.

All three interventions are based on the standard PA approach, which means that it is possible to convert a PSPA or SPAIRE approach to a standard PA if required during surgery - a risk mitigation option which is available in standard care as well as in this trial.

A robust safety reporting procedure will be implemented (see section 7) such that adverse events will be detected and managed appropriately, according to established standard operating procedures.

2.1 Medical Physics Expert (MPE) report

The total radiation dose that a patient participating in this trial will receive is 3.7mSv of which 0mSv is in addition to standard care.

The lifetime risk of developing a cancer resulting from images taken as part of the routine clinical care is 1 in 5,000 for a 40 year old patient, this would fall to 1 in 10,000 for a 60 year old patient. For the ages of the expected cohort in this trial, this is considered to be a minimal risk [26, 27] and is equivalent to around 1.5 years of natural background radiation in the UK.

This assumes that the following medical imaging is undertaken:

- Pre-operative spiral CT scan (MAKO protocol) and AP X-ray of the left and right hip
- Post-operative AP and lateral X-ray of affected hip.

3 AIMS, OBJECTIVES AND OUTCOMES MEASURES

The primary aim of this trial is to investigate whether two novel robotic-assisted tendon-sparing posterior approaches (PSPA and SPAIRE) improve patient outcomes in THR compared with a robotic-assisted standard posterior approach (PA). Only patients undergoing cementless THR will be considered for the trial.

3.1 Primary objective

The primary objective is to determine whether there is a clinically significant between-group difference comparing PSPA vs PA, and SPAIRE vs PA for THR patients using the Oxford Arthroplasty Recovery Score (OARS) PROM at 6 weeks post-operatively, and to estimate the magnitude of any differences.

3.1.1 Estimands framework

Target population	Anyone with OA of the hip requiring a total hip replacement. The trial will focus on patients suitable for a cementless acetabular component as this is appropriate for robotic guided surgery, but it will be possible to generalise the outcomes to THR procedures more generally.
Variable of interest	The primary outcome is the OARS PROM at 6 weeks post-operatively
Key intercurrent events	1. Death: while alive policy: data collected up to point of death 2. Treatment switching: participant receives a hip replacement that is not the one they were allocated to (due to error or surgical decision at point of treatment): (a) treatment policy: data analysed as though intercurrent event did not occur (b) principal stratum: data analysed for the known subpopulation of participants who received their procedure as allocated 3. Failure of treatment initiation: participant does not receive hip replacement at all (participant characteristics, service delivery issues): (a) treatment policy: cannot be applied to OARS, as only applicable post-operatively (can be applied to secondary outcomes as appropriate) (b) principal stratum: data analysed for the known subpopulation of participants who received their procedure as allocated (assumed that failure of receipt of THR would apply regardless of allocated treatment)
Population-level summary of variable	Between-group mean difference for OARS at 6 weeks post-operatively: (i) PSPA vs PA; (ii) SPAIRE vs PA

3.2 Secondary objectives

- To compare (i) PSPA vs PA and (ii) SPAIRE vs PA in terms of muscle damage and global inflammation using serum creatine kinase (CK), and C-reactive protein (CRP) blood biomarkers pre-operatively, and at day 0/1 and 6 weeks post-operatively.
- To compare (i) PSPA vs PA and (ii) SPAIRE vs PA in terms of participant walking (average mean daily steps, mean step rate, and mean and maximum walking bout time), and sleep parameters (mean daily sleep time, and mean daily sleep quality) measured via an activity monitor worn for 2 weeks pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks).
- To compare (i) PSPA vs PA and (ii) SPAIRE vs PA in terms of the Oxford Arthroplasty Early Change Score (OACS) PROM at 6 weeks post-operatively, and to estimate the magnitude of any differences.
- To compare (i) PSPA vs PA and (ii) SPAIRE vs PA using the Self-Administered Patient Satisfaction Scale (SAPS) PROM post-operatively at 6 weeks, 6 months (26 weeks) and 12 months (52 weeks), and the Oxford Hip Score (OHS), Lower Extremity Functional Scale (LEFS) and EQ-5D-5L PROMs pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks).
- To compare the trajectory of outcome measures between SPAIRE, PSPA, and PA, and evaluate whether there are differences in outcomes over time in terms of participant walking (average mean daily steps, mean step rate, and mean and maximum walking bout time), and sleep parameters (mean daily sleep time, and mean daily sleep quality) measured via an activity monitor worn for 2 weeks pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks). This is also evaluated in terms

of participant pain, function, activity, general health status and satisfaction using the Self-Administered Patient Satisfaction Scale (SAPS) PROM post-operatively at 6 weeks, 6 months (26 weeks) and 12 months (52 weeks), and the Oxford Hip Score (OHS), Lower Extremity Functional Scale (LEFS) and EQ-5D-5L PROMs pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks).

- To compare differences between (i) PSPA vs PA and (ii) SPAIRE and PA in terms of clinical outcomes intra-operatively (duration of surgery; blood loss), and length of hospital stay.
- To compare differences between (i) PSPA vs PA and (ii) SPAIRE vs PA in terms of pain medication used in addition to the standardised prescribed post-surgery medication, immediately post-surgery and 6 week post-operatively.
- To evaluate safety of PSPA and SPAIRE approaches with respect to the PA via recorded adverse events from the day of surgery until 12 months (52 weeks) post-operatively via medical notes and post-operative follow-up at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks).

3.3 Primary outcome

The primary outcome measure is the OARS PROM [28], which will be measured at 6 weeks post-operatively to assess participants' perceptions relating to the surgical process and early recovery period following surgery. The OARS is a 14-question PROM that includes four domains: pain; sleep; nausea and feeling unwell; and mobility. Each item has five options from which the patient is invited to select one answer: strongly disagree; disagree; neither agree nor disagree; agree; strongly agree.

The OARS PROM is validated for use at 6 weeks-post operatively only, hence is not used at any other time point. Also, OARS, as a purely post-operative outcome measure, is only relevant in participants who undergo THR, so should any randomised participants not receive THR, they will not be able to complete OARS.

3.4 Secondary outcomes

3.4.1 Blood biomarkers

Muscle damage and global inflammation will be assessed through measurements of serum creatine kinase (CK), and C-reactive protein (CRP) [29, 30] via a blood test pre-operatively at admission, and at day 0/1 and 6 weeks post-operatively.

Serum creatine kinase (CK) has been used as a measure of muscle damage following THR surgery, and C-reactive protein (CRP) levels have been used as a measure of global inflammation [29].

The proposed 3-arm trial design investigating three posterior approaches with progressive levels of tendon-sparing provides a unique opportunity to investigate the association of muscle damage and inflammation on other outcome measures, and the potential for such biomarkers as early indicators of recovery and rehabilitation.

3.4.2 Physical activity monitoring

The inclusion of physical activity monitoring will provide quantitative data to assess whether tendon-sparing approaches lead to an improvement in walking and sleep outcomes. Participant physical activity will be measured via an activity monitor worn for two consecutive weeks pre-operatively, and post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks). Specifically, the following outcomes will be derived and analysed:

- Mean daily steps (total steps)
- Mean daily step rate (steps/min) during walking
- Mean and maximum daily walking bout time (minutes)
- Mean daily sleep time (minutes)
- Mean daily sleep quality (defined as the percentage of total sleep time divided by the total time between going to bed and getting up. This accounts for periods of unrest or rising during the overall sleeping period.)

The activity monitors will not capture any personal identifiable data; a unique monitor ID number will be used to issue a monitor to a participant at the different data capture periods. When returned following a data collection period, each monitor will be wiped with an alcohol wipe, washed in soapy water and dried. The raw accelerometry data will be downloaded to an NHS laptop by a blinded member of the site Research Team. The activity monitor will then be charged ready to be issued again. A log of monitor usage will be maintained by the Trial Manager, which will record the monitor ID against each participant for each data collection period, along with the date of issue, and return. This will ensure that the use of monitors is tracked by the site Research Team, and reminders can be sent as required if a monitor is not returned following a data collection period.

The raw accelerometry data will be processed to provide an event data summary file using algorithms validated by the activity monitor manufacturer. This file summarises activities based on activity level, and includes walking (including a step count), and sleeping events, and the time periods over which they occur. From this event data summary, further custom processing will be completed by the Co-CI using existing scripts to determine the above outcome measures. The processed activity metrics will then be uploaded to the REDCap database.

3.4.3 PROMs

Participants will be asked to compete the following six PROMs:

- Primary outcome measure to be completed post-operatively at 6 weeks:
  - OARS
- Secondary outcome measure to be completed post-operatively at 6 weeks:
  - OACS
- Secondary outcome measure to be completed post-operatively at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks):
  - SAPS
- Secondary outcome measures to be completed pre-operatively, and post-operatively (or following scheduled date of surgery if surgery does not take place) at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks):
  - OHS
  - LEFS
  - EQ-5D-5L (to assess general health and quality of life)

PROMs collected pre-operatively and post-operatively at 6 weeks are to be completed by the participant during the face-to-face clinic visit with the site Research Team. PROMs collected at 6 months (26 weeks) and 12 months (52 weeks) post-operatively will be collected electronically, via survey invitations sent by ExeCTU. However, if a participant has opted to complete the PROMs on paper, these will be posted out to them at these time points by the site Research Team. The NJR has shown that the maximal improvement in pain and function post THR occurs 12 months (52 weeks) post-surgery, hence the choice of these time points for outcome assessment [31].

3.4.4 Clinical outcome measures

Clinical outcome measures include length of hospital stay, surgery time, blood loss and analgesic use. Analgesic use is defined as the quantity and duration of analgesia required in the immediate period 6 weeks post-operation. Participants will be discharged from hospital with a routine, set amount of analgesia as per hospital protocols. These medications are listed below:

- 12 days of Paracetamol 1g
- 5 doses of twice daily Celecoxib 200mg
- 5 doses of 10mg Oxycodone MR to be used twice a day
- 5 doses of 5mg Oxycodone IR to be used as required (and maximum four times a day)
- 5 days of 30mg Codeine Phosphate to be used as required and maximum 4 times a day (once Oxycodone course has finished)

Participants will be asked at their 6 week post-operative visit if any additional analgesia, in addition to the above prescription, was used immediately post-surgery up to 6 weeks post-operatively, either purchased over-the-counter without prescription or via GP prescription. This will be a yes/no answer, and the site Research Team will record the names of any additional analgesia in a free text box in the eCRF. Doses of analgesia will not be collected as patient recall is likely to be inaccurate, according to our PPIE representatives on the TMG.

3.5 Table of endpoints/outcomes

Objective	Outcome Measures	Time point(s) of evaluation of this outcome measure
Primary objective		
To test whether the SPAIRE and PSPA provide benefits to participants compared to the PA	OARS PROM	6 weeks post-operatively
Secondary objectives		
To compare differences between PSPA and PA, and between SPAIRE and PA in terms of participant muscle damage and global inflammation	Blood biomarkers CK and CRP	At pre-operative assessment (baseline), and at day 0/1 and 6 weeks post-operatively
To compare differences between PSPA and PA, and between SPAIRE and PA in terms of walking and sleep	Activity monitoring based on 2 weeks' continuous data collection: • Mean daily steps • Mean step rate • Mean walking bout time • Maximum walking bout time • Mean daily sleep time • Mean daily sleep quality	At pre-operative assessment (baseline), and at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks) post-operatively
To compare differences between PSPA and PA, and between SPAIRE and PA in terms of PROMS	OACS	6 weeks post-operatively

To compare differences between PSPA and PA, and between SPAIRE and PA in terms of PROMS	Participant satisfaction: • SAPS	At 6 weeks, 6 months (26 weeks), and 12 months (52 weeks) post-operatively

To compare differences between PSPA and PA, and between SPAIRE and PA in terms of PROMS	Pain, function, activity and mobility, and general health status and quality of life: • OHS • LEFS • EQ-5D-5L	At pre-operative assessment (baseline), and at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks) post-operatively
To compare the trajectory of outcome measures between SPAIRE, PSPA, and PA, and evaluate whether there are differences in outcomes over time	Activity monitoring based on 2 weeks' continuous data collection: • Mean daily steps • Mean step rate • Mean walking bout time • Maximum walking bout time • Mean daily sleep time • Mean daily sleep quality Pain, function, activity, general health status, and satisfaction: • OHS • LEFS • EQ-5D-5L • SAPS	6 weeks, 6 months (26 weeks), and 12 months (52 weeks) post-operatively
To compare differences between PSPA and PA, and between SPAIRE and PA in terms of clinical outcomes during and immediately following surgery	• Duration of surgery • Blood loss • Length of hospital stay	Intra-operatively (duration of surgery; blood loss) Until time of hospital discharge (length of hospital stay)
To compare differences between PSPA and PA, and SPAIRE and PA in terms of pain medication used in addition to the standardised prescribed post-surgery medication, immediately post-surgery and 6 weeks post-operatively	• Additional over-the-counter or prescribed analgesia needed during the first 6 weeks post-operative? (Yes/No and list any additional medication)	6 weeks post-operatively
To evaluate the safety of PSPA and SPAIRE approaches with respect to the PA	Adverse events recorded from the day of surgery	Until 12 months (52 weeks) post-operatively via medical notes and post-operative follow-up at 6 weeks, 6 months (26 weeks), and 12 months (52 weeks)

4 TRIAL DESIGN

The trial is a single-centre, double-blind, parallel, three-arm, randomised-controlled, superiority trial.

4.1 Trial setting

The trial will be run at the Royal Devon and Exeter Hospital (Wonford) (RDE), which encompasses the Nightingale Hospital Exeter (NGE) surgical site, under the Royal Devon University Healthcare NHS Foundation Trust (RDUH), which is a centre of excellence for hip arthroplasty. The CI Mr Al-Amin Kassam will also act as the site Principal Investigator (PI).

4.2 Participant eligibility criteria

4.2.1 Inclusion criteria

- Patients with osteoarthritis of the hip
- Patients suitable for a cementless acetabular component
- Patients over the age of 18 years
- Patients of any Body Mass Index (BMI)
- Patients willing and able to provide informed consent in English

4.2.2 Exclusion criteria

- Patients with active systemic or local infection that would preclude standard THR surgery
- Patients undergoing bilateral THR in same operative episode
- Patients unable to give informed consent
- Patients unable or unwilling to take part in the trial process, including patients unable to undertake activity monitoring data collection or complete the PROMs questionnaires in English[1]

5 TRIAL TREATMENTS

The trial is designed to compare each of two tendon-sparing PAs for THR (PSPA and SPAIRE) with the standard PA for a range of outcomes including PROMs, physical activity monitoring, clinical biomarkers (CK and CRP) and clinical outcomes. Participants will be randomised to one of three groups (1:1:1). Group 1 of the trial (control group) will receive THR with the current gold standard PA, in which three tendons are released. Group 2 will receive THR with a PSPA, in which two tendons are released. Group 3 will receive THR with a SPAIRE approach in which one tendon is released. All participants will receive THR using MAKO robotic guidance. This will allow consistent positioning of the hip replacement components across all trial groups, allowing the effect of reducing the number of tendons released to be more reliably investigated. All other pre-, peri-, and post-operative aspects of care will be the same for all participants. All participants will receive routine anaesthetic, as per standard care provided during THR procedures.

If the trial treatment allocation needs to be converted during surgery, the surgeon must clearly document this on the intra-operative data collection form and the reasons why treatment allocation was not received.

[1] English is the only common translation available in official translations of all six PROMs

5.1 Preoperative imaging and surgical planning (all participants)

As part of the routine MAKO planning procedure, participants in all three groups will have a spiral CT scan and an AP x-ray of the left and right hip. As MAKO surgery is performed routinely for elective THR at the RDE trial, trial-specific informed consent will not be required before this imaging is performed. Imaging will be undertaken according to the needs of the MAKO system and a three-dimensional plan will be made for the surgeon for every participant. This will be done prior to surgery, but **no more than 3 months** before the planned date of surgery to minimise change due to disease progression. The CT for the planning procedure will not determine or affect a patient's eligibility for involvement in the trial.

In order to produce the plan, the CT and x-ray images will be sent to Stryker, US. These images will contain at least two identifiers (for example, name, hospital number or date of birth), but these will only be seen by employees of Stryker and will not be shared with any other party. This transfer of data has been approved by RDUH governance and is a secure means of transferring data. It is used for all patients undergoing MAKO THR as part of routine clinical practice; this includes all patients who are not involved in the research trial.

If, for unexpected reasons, the surgery is delayed such that the CT scan was performed more than 3 months before the actual date of surgery, then the surgeon will make a clinical decision whether to accept the use of the completed CT or to repeat the scan, according to their normal clinical practice. This will be recorded but will not constitute a protocol deviation and the patient will remain in the trial.

The plan provided by Stryker will describe the optimal implant size and position for restoration of leg length, offset, hip centre of rotation and stability. This will be provided for all participants, regardless of treatment allocation. During the operation, the surgeon may make adjustments to this according to their normal practice in any of the trial arms.

5.2 Surgical expertise

It is a prerequisite that all treating surgeons listed on the trial delegation log have been trained to use the MAKO system, have performed a sufficient number of robotic-assisted THR procedures outside of the trial, and are familiar with the technique.

Surgeons will only be eligible to perform trial cases when they have completed the MAKO hip training course (Stryker will provide evidence to the trial team), have performed at least 12 MAKO hip cases outside of the trial, thus completing the learning curve for the MAKO robot, and they and the CI are confident that they are familiar with the technique.

Because participants in all three groups are receiving a version of the posterior approach with or without tendon preservation, if there is a clinical need to release more tendons to perform surgery safely this can be undertaken by the operating surgeon. The most common reason for conversion is if surgical exposure is insufficient and further tendon release is required to improve visualisation of the acetabulum to enable preparation and implantation of the acetabular component. This is likely to take the form of releasing one or two further tendons to improve surgical exposure. The data of any conversions will be collected; treatment switching will be accounted for using sensitivity analyses as per the estimands framework.

Surgery will be performed by seven Consultant orthopaedic surgeons in the Exeter hip unit who all have a similar experience of all three THR approaches and also the use of the MAKO robot. Only these named surgeons will perform the surgery and we do not anticipate any new surgeons joining the Research Team during the trial. The clinical team feel that there is minimal variability between

surgeons with regard to their ability in performing all three THR interventions, in terms of their patient outcomes as highlighted in the National Joint Registry.

5.3 Group 1 – THR with the standard PA and robotic guidance (Control Group)

Participants will receive a THR using the PA in which three tendons are released to access the hip joint (piriformis, obturator internus, and obturator externus). An attempt is routinely made to repair these tendons after implantation of the hip replacement components. This is the current approach used in the majority of THR procedures in the UK. Robotic guidance using the MAKO robotic system will ensure that the acetabular cup component is accurately positioned in the surgically planned position during surgery.

5.4 Group 2 – THR with the PSPA and robotic guidance (Intervention Group A)

Participants will receive a THR using the PSPA in which two tendons are released to access the hip joint (obturator internus and obturator externus). These are repaired once the hip replacement components have been implanted. This approach is the most commonly used approach by surgeons in Exeter currently. This approach has been previously shown in an RCT to limit access and visibility of the hip joint compared with the PA and presents a greater challenge in accurately positioning the acetabular component [21]. Robotic guidance using the MAKO robotic system will ensure that the acetabular cup component is accurately positioned during surgery.

5.5 Group 3 – THR with the SPAIRE approach and robotic guidance (Intervention Group B)

Participants will receive a THR using the SPAIRE approach in which only one tendon is released to access the hip joint (obturator externus). This tendon is repaired once the hip replacement components have been implanted. This approach has been previously used but limits access and visibility of the hip joint, compared with both the PA and PSPA, and presents a greater challenge in accurately positioning the acetabular component. Robotic guidance using the MAKO robotic system will ensure that the acetabular cup component is accurately positioned during surgery.

5.6 Post-surgical rehabilitation programme

Post-operative rehabilitation will be provided as per NHS standard care for THR, which comprises daily physiotherapy provided post-operatively for the duration of each participant's stay in hospital. The routine Outpatient clinic follow-up appointment at 6 weeks post-operatively includes a review by a physiotherapist, advice on post-operative activity and a home exercise programme. Additional outpatient physiotherapy requests are made by clinicians on case-by-case basis according to clinical need.

6 RECRUITMENT, RANDOMISATION AND BLINDING

6.1 Participant identification

The trial will recruit adult patients undergoing elective THR surgery due to osteoarthritis of the hip. The RDE completes approximately 800 elective primary THR procedures each year, from which the trial participants will be recruited.

The MAKO robotic guidance system currently only supports the use of cementless hip socket components, hence all patients will be assessed for their suitability for a cementless socket component based on the quality of their bone stock determined from pre-operative plain radiographs. Only once eligibility for robotic surgery has been determined and consented for, will the CT scan be requested and performed, in line with current local clinical practice.

There are two ways in which potentially eligible patients will be identified:

- If a patient has already been listed for THR surgery using the MAKO system then they will appear on a waiting list trawl done by a member of the Direct Care Team using the RDUH EPIC system. This will be repeated regularly throughout the trial to ensure maximum identification of all eligible patients. The EPIC records of each patient will be reviewed against the trial inclusion and exclusion criteria by a clinician. Patients under the age of 65 will be contacted by a member of the Direct Care Team and asked for permission for a member of the site Research Team to post or email a Patient Information Sheet (PIS) to them. The records and X-rays of patients over the age of 65 years will be further reviewed by a surgeon to confirm whether or not they may be suitable for a cementless socket and therefore are potential participants. Those who are suitable will then follow the above process. The age of 65 has been selected as patients under 65 have been shown to potentially have lower revision rates using uncemented acetabular components in the NJR. Patients above 65 can benefit from cemented or uncemented acetabular components depending on the clinical records and radiographs and so the decision of which component should be used, and therefore whether MAKO robotic surgery can be used, will be determined by the treating clinical team.

- If a patient has not yet been listed for THR surgery, the trial can be introduced to them by their clinician during their routine Outpatient Assessment Clinic, once the clinician has reviewed and assessed the patient against the trial inclusion and exclusion criteria. The patient will be asked for permission for a member of the site Research Team to post or email a PIS to them. This is to be clearly documented by the clinician on EPIC.

The site Research Team will schedule a phone call to the patient within 2 weeks of sending the PIS to see if they have read and understood it, if they are interested in taking part in the trial and to answer any questions the patient might have. If the patient is agreeable, a member of the site Research Team will arrange to meet them to discuss the trial further at either their routine Surgical Consenting Clinic or Pre-Operative Assessment appointment, and take informed consent to the trial should the patient agree to participate.

Final confirmation as to whether the surgical interventions involved in the trial are appropriate to the participant will be made at the regular hip Multidisciplinary Team meeting (MDT) in the week prior to surgery. If the participant is deemed unsuitable for the trial intervention(s), they will be informed by phone to discuss this and will be withdrawn from the trial (see section 6.8). If the participant is deemed suitable, they will continue to the randomisation stage. A withdrawal for clinical reasons such as this is felt to be unlikely but may be due to rapid deterioration in the hip osteoarthritis which may deem more complex reconstruction of the hip to be required rendering the participant no longer eligible for the study.

6.2 Screening

Data on the recruitment process will record the number of patients:

- Identified from the initial screening (Direct Care Team)
- Receiving a Patient Information Sheet (site Research Team)
- Who express an interest in participating during the follow up phone call (site Research Team)
- Who are seen in the Surgical Consenting Clinic or Pre-Operative Assessment (site Research Team)
- Who are consented (site Research Team)

At each point, the reason for ineligibility, where known, will be recorded on the REDCap screening log.

Ethnicity data collection for all screened patients will be performed by using the SlicerDicer function on EPIC. This data will be collected anonymously at the end of the recruitment period, or upon request prior to that time point, if required.

6.3 Informed consent

The CI will have overall responsibility for the conduct of research during the trial at the site. This includes ensuring that any site Research Team member delegated to take informed consent has received the appropriate training and is included on the delegation log. This includes Assistant Research Practitioners, Research Practitioners, Research Nurses, Research Co-ordinators and clinicians.

Members of the site Research Team approved to take informed consent will arrange to meet with the patient at either routine Surgical Consenting Clinic or Pre-Operative Assessment appointment. During this appointment the trial will be spoken about in depth, giving the patient the opportunity to ask questions they have concerning trial participation. The patient will decide whether or not they wish to take part, and if they agree to participate they will be asked to provide their written consent using the trial Informed Consent Form (ICF). The site Research Team will explain to the patient that participating in the trial is entirely voluntary and that they have the right to withdraw at any time without needing to provide any reason, or they have the option to flexibly change their participation in the trial by selectively reducing or ceasing any or all of the aspects listed in section 6.8. They will reassure the patient this will in no way prejudice their further treatment.

When completing the ICF, the patient will be asked to read each statement and initial in the relevant boxes if agreeable; they will then sign, print name and date the form, as will the person taking consent. The participant will be given a copy of the signed ICF for their records, a copy will be uploaded to the patient's electronic medical notes on EPIC, and the original will be filed in the Investigator Site File (ISF) held in the site office. The consent discussion will be documented in the patient's electronic medical notes on EPIC by the person who took consent, and the patient will be linked to the trial on EPIC. This will generate an automatic notification to the site Research Team once the patient has been given a surgery date. As per current procedure in the hip unit, time between surgical consent (and therefore trial consent) and surgery is likely to be up to 2-3 months with obviously some surgical administrative variance. The Research Team will also be in communication with the participant's Consultant secretary who will be made aware they need to inform the Research Team once they have given the participant a surgery date also. The Research Team will then be able to plan ahead when the participant is to be randomised.

The participant's GP will be informed of their inclusion into the trial. In addition, once the trial has ended, the GP will be sent a letter notifying them of the treatment allocation received by the participant; please refer to section 6.11 detailing what defines the end of the trial.

A patient is required to reconfirm ongoing participation in the trial if there is a delay of greater than 3 months between consent and date of surgery. The site Research Team will first check if the patient is still happy to continue their involvement in the trial, and if so obtain reconfirmation accordingly. Reconfirmation can either be taken verbally via telephone, or in person at a routine hospital appointment. The Research Team will document this in the patient's medical notes. If the patient no longer wishes to take part in the trial, they can either ask to selectively reduce their participation or fully withdraw from the trial.

When a patient consents to the trial, they will be asked whether they would like to be kept informed about developments of the trial. At the end of the trial all participants will receive a letter notifying them of the treatment allocation they received.

6.4 Participant expenses

The face-to-face visit at 6 weeks post-surgery is part of usual NHS practice. The follow-up visits at 6 months (26 weeks) and 12 months (52 weeks) are both planned to be delivered remotely. Therefore, there is no additional payment for trial participation in terms of travel expenses.

6.5 Randomisation

Participants will be randomised in a 1:1:1 ratio to SPAIRE:PSPA:PA by the ExeCTU. To promote balance across participant characteristics thought to be predictive of outcome, minimisation with a random element will be used. Characteristics of sex (male; female), age (<50; ≥50 years) and BMI (<30; ≥30 kg/m^2) will be used in the minimisation algorithm (i.e. a total of eight combinations of minimisation factors). The operating surgeon will not be included as a minimisation factor (due to anticipated low inter-operator variability (discussed in greater detail in section 5.2), plus concern that the number of combinations of minimisation factors would be too high if surgeon is included as a factor) but a sensitivity analysis will be performed for the primary outcome measure, to investigate any operator effects.

Participants will be randomised via REDCap within 7 days prior to surgery. Randomisations will be performed, so far as is practically feasible, in strict order by date of scheduled surgery; if more than one participant is scheduled for surgery on the same date, the participants will be randomised in order of age (older age randomised first); if there is more than one participant with the same date of birth they will be randomised in alphabetical order of surname. The member of the site Research Team performing the randomisation will be unaware of previous allocations. If any cases are scheduled at short notice, for various clinical or administrative reasons, then randomisation will be performed as close to 7 days prior to their date of surgery as possible, although this may result in randomisations being performed out of order by date of scheduling. The surgeon and theatre team will still be informed within 24 hours of surgery. If a patient has surgery rescheduled after they have been randomised within 7 days prior to surgery (usually to last minute urgent or trauma cases), their randomisation will be retained. The patient's surgery will be rescheduled for as close as possible to their original date and surgeon/clinical team informed of the randomisation group within 24 hours prior to surgery. The Research Coordinator, Senior Trials Administrator and Team Lead at site will be unblinded and they will be notified of randomised allocation directly from REDCap immediately on randomisation being performed, within **7 days prior to surgery**. The operating surgeon and allocated members of theatre staff will be notified of the randomised allocation directly from REDCap within **24 hours prior to surgery**. This schedule for randomisation is intended to minimise post-randomisation attrition. Please refer to Table 1 in section 6.6 for summary.

In the event that a participant has been randomised and their planned surgery does not go ahead or they change their mind about participating in the trial, the site Research Team will notify the Trial Manager immediately.

6.6 Blinding

The trial will be double-blinded; the participants will be unaware of which type of surgical approach they have received, and identified members of the site Research Team, which will include the Research Nurse and Research Practitioners who collect outcome data, will also be blinded to the allocated group. Surgeons will remain blinded until the randomisation email is received within **24 hours of surgery**. Operating surgeons will not be involved in collecting any post-operative data. A Senior Statistician will be unblinded throughout the trial to facilitate provision of unblinded reports to the DMC. Blinding of the analysing statistician will be considered, using the Blinding of Trial Statisticians (BOTS) guidance [32]. Use of the BOTS tool will allow a more thorough understanding

of the risks of unblinding of the analysing statistician. However, the default position for the trial will be that the trial statistician (performing data analysis) will remain blinded until the presentation of the primary analyses of the primary and secondary outcome data. At this point, the wider trial team will be unblinded. The remaining analyses will then be performed with the statistician unblinded. Any deviation from this position will be made in the light of the risk assessment derived from the BOTS tool. The Research Coordinator, Senior Trial Administrator and, by means of contingency, the Research Team Lead, will be unblinded and will randomise participants via REDCap within **7 days prior to surgery**; they will also enter the surgical data to the trial database. Post-operative care does not differ between each technique, and the surgical dressing is applied to the same site over the hip area and cannot be distinguished between each approach. The documentation about the surgical approach in the operation notes will not specify which technique was used for the procedure and will state that the patient is enrolled in the HIPSTER research trial. Table 1 below summarises the planned blinding status for key personnel.

Table 1: Blinding status to individual participant treatment allocations

BLINDED	Notified of treatment allocation when?	How?
Participants	At end of trial (as defined in section 6.11), if requested.	Via letter from site Research Team
Site Research Team* (co-ordinating follow-ups)		
Surgeon	Up to 24 hours prior to surgery	Automatically via REDCap
Trial Statistician	To be unblinded to participant allocations following presentation of primary analyses	Unblinding to take place during meeting where results are presented, by unblinded member of trial team who is aware of group allocations
UNBLINDED		
Research Coordinator (RDE)/Trial Manager (no post-op data collection or involvement)	Up to 7 days prior to surgery	Automatically via REDCap
Site Senior Research Administrator (RDE)	Up to 7 days prior to surgery	Automatically via REDCap
Site Research Team Lead (RDE)	Up to 7 days prior to surgery	Automatically via REDCap
Senior Statistician		

*Research Nurse, Research Practitioners

The week prior to surgery, the hip Multidisciplinary Team will meet to discuss the following week's surgical cases. In this meeting, patients will be identified as participants in the HIPSTER trial; however, no information regarding the trial treatment arm will be discussed. The operating surgeon will receive the treatment allocation via an email from REDCap within 24 hours of surgery. The theatre team will be made aware of a participant's randomised allocation within 24 hours of surgery by the operating surgeon. The theatre kits for the SPAIRE, PSPA and PA approach will always be available in theatre and therefore the theatre team will not need to be notified more than 24 hours prior to surgery and can remain blinded until that point.

6.6.1 Emergency unblinding

We do not expect a situation to arise where knowledge of exact surgical technique used will be needed to inform any urgent medical management. As such, no special emergency unblinding process is required, but surgical details can be obtained within normal working hours from the site Research Team.

6.7 Trial assessments

6.7.1 Schedule of events

Assessment/visit	Time point								
	Pre-op				Post-op				
	Screening	Pre-op assessment (baseline)	7 days prior to surgery (Research Team)	24 hours prior to surgery (Surgeon & theatre staff)	Day 0/1 (inpatient)	Notes review after discharge	6 weeks (+/- 2 weeks)	6 months (26 weeks) (-4 weeks/+12 weeks)	12 months (52 weeks) (-4 weeks/+12 weeks)
Check eligibility and provide PIS	X								
Confirm inclusion/exclusion criteria		X							
Consent		X							
Demographic data (name, DOB, sex of patient, height, weight, BMI, ethnicity), any existing comorbidities, and contact details		X							
Blood biomarkers – CK and CRP		X			X		X		
Activity monitor issued *in clinic* and prepaid returns envelope provided		X					X		
PROMs – OHS, LEFS, EQ-5D-5L *in clinic*		X							
Randomisation			X	X					
Check pre-operative imaging has been requested by surgeon (imaging to be done within 3 months of surgery date)		X							
Peri-operative data: length of stay[1], surgery time, blood loss, conversion of allocated randomisation approach[2]						X			
PROMs – OARS, OACS, OHS, LEFS, EQ-5D-5L, SAPS *in clinic*							X		
Activity monitor issued *via post* and prepaid returns envelope provided								X	X
PROMs – OHS, LEFS, EQ-5D-5L, SAPS *remotely*								X	X
Additional analgesia use							X		
Safety reporting – AEs and SAEs					X	X	X	X	X
Additional surgical procedures								X	X

[1]Length of stay is recorded at time of discharge, i.e. number of nights a participant stays in hospital post-surgery. [2]Conversion of approach records if the intended approach is converted to another during surgery (SPAIRE to PSPA or PA; or PSPA to PA).

6.7.2 Screening and confirmation of inclusion/exclusion criteria

Patient eligibility is checked by a clinician in the Direct Care Team at the time of surgery listing or through reviewing of the existing surgical waiting list. Their eligibility is confirmed by a member of the site Research Team prior to the patient providing informed consent at either their Surgical Consenting Clinic or Pre-Operative Assessment. This is also reconfirmed at the pre-operative MDT a week prior to surgery.

6.7.3 Pre-operative/baseline time point

Patient seen in clinic by site Research Team to discuss trial and provide informed consent.

Demographic data to be collected:

- Name
- Date of birth
- Sex of patient
- Height (cm)
- Weight (kg)
- BMI

Participant contact details to be collected and preference of communication e.g. telephone, email, post.

PROMs data to be collected for:

- OHS
- LEFS
- EQ-5D-5L

Physical activity monitor and instructions to be issued for participant to wear for two consecutive weeks, and a prepaid returns envelope provided. All activity monitors will be returned to the Hip Office, Princess Elizabeth Orthopaedic Centre at the RDE and collected periodically by the Co-CI to download the data.

Collect blood sample to measure CK and CRP biomarkers.

Ethnicity and details of any existing comorbidities to be collected from the medical notes.

Randomisation to allocated treatment arm via REDCap; site Research Team to be informed within 7 days prior to surgery; surgeon to be informed within 24 hours of surgery.

6.7.4 Peri-operative time point

- Retrospective data collection from participant medical notes review on EPIC and subsequent entry into REDCap for:
- Surgery time – this will be defined from the time that surgical incision was made through to time that the wound dressing was applied at the end of the surgical procedure
- Blood loss – this will be an estimate of blood loss (mls) made by the surgical and anaesthetic teams
- If there has been a conversion from allocated randomised approach – this will be documented and the reason for conversion also documented

Report any AEs/SAEs that have occurred during surgery.

6.7.5 Day 0/1 post-operative time point (inpatient)

Participant seen on ward by either a member of the site Research Team (if surgery performed at RDE) or qualified Healthcare Professional (if surgery performed at Nightingale Hospital Exeter (NGE) to collect blood sample to measure CK and CRP biomarkers.

Review of electronic patient records (EPIC) by site Research Team for AEs/SAEs that occur during inpatient stay. (EPIC is available at RDE and NGE).

Length of stay recorded upon discharge; this will be measured in terms of number of nights stayed in hospital post operatively.

6.7.6 6 weeks post-operative time point

Participant seen in routine orthopaedic Outpatient clinic by site Research Team.

PROMs data to be collected for:

- OARS
- OACS
- OHS
- LEFS
- EQ-5D-5L
- SAPS

Physical activity monitor and instructions to be issued for participant to wear for 2 consecutive weeks, and a prepaid return envelope provided.

Collect blood sample to measure CK and CRP biomarkers.

Record if participant has taken any additional analgesia other than the prescribed post-surgery analgesia (yes/no). If yes, note whether this was purchased over-the-counter without prescription or via GP prescription, and record details in a free text box in the eCRF. Report any AEs/SAEs that have occurred from point of surgery to 6 weeks post-operatively.

6.7.7 6 months (26 weeks) post-operative time point

Remote follow-up by ExeCTU and site Research Team.

Electronic survey invitations for PROMs will be sent to participants directly from ExeCTU:

- OHS
- LEFS
- EQ-5D-5L
- SAPS

Participants who have opted for paper PROMs will have these posted to them by the site into REDCap by the blinded members of the site Research Team.

Physical activity monitor and instructions to be issued via post for participant to wear for two consecutive weeks, and a prepaid return envelope provided.

Report any AE/SAEs, and document any additional surgical procedures that have occurred within 6 to 26 weeks post-operatively; this is done via telephone call or email to participant. Participant will be reminded to return activity monitor. Medical notes also to be reviewed for any SAEs.

6.7.8 12 months (52 weeks) post-operative time point

Remote follow-up by ExeCTU and site Research Team.

Electronic survey invitations for PROMs will be sent to participants directly from ExeCTU:

- OHS

- LEFS
- EQ-5D-5L
- SAPS

Participants who have opted for paper PROMs will have these posted to them by the site Research Team, with a prepaid return envelope provided.

Physical activity monitor and instructions to be issued via post for participant to wear for 2 consecutive weeks, and a prepaid return envelope provided.

Report any AE/SAEs, and document any additional surgical procedures that have occurred within 26 to 52 weeks post-operative; this is done via telephone call or email to participant. Participant will be reminded to return activity monitor. Medical notes also to be reviewed for any SAEs.

6.8 Withdrawal and change to participation status

Participants have the right to withdraw at any time during the trial without prejudice to their clinical care and there is no obligation to provide reasons for withdrawal. At the time of providing informed consent, participants must be made aware that they need to contact the site Research Team should they no longer wish to participate in the trial. For each withdrawal or change in participation status, the withdrawal log on REDCap is to be completed by a member of the site Research Team, which will trigger a notification to the Trial Manager that a participant has been withdrawn, and the reason why (if provided).

Participants will be able to flexibly change their participation in the trial by selectively reducing or ceasing any or all of the following aspects:

- Use of the physical activity monitor at any time point, pre- and post-operatively
- Collection of blood biomarkers at any point pre- and post-operatively
- Completion of PROMs data at any time point, pre- and post-operatively
- Passive data collection from routine medical records (except where required for reporting of serious adverse events or for monitoring purposes)

In the event of a withdrawal or change of participation status, any available details for the reason of withdrawal should be documented in the participant's medical notes, in the eCRF, and in the investigator site file. Clarification on the nature of withdrawal of consent, as outlined above, should be sought. Allowing flexibility in participation status will protect the rights and wellbeing of the participants while maximising the opportunity to collect important outcome data and limit research waste.

If a participant withdraws their consent prior to randomisation, or if excluded on the grounds of ineligibility post-consent but prior to randomisation, they will be withdrawn from the trial (i.e. no further data collection); the data collected up until the point of withdrawal will still be available for use in trial reporting. The site Research Team will endeavour to replace such participants.

If a participant wishes to withdraw post-randomisation and prior to surgery, then the participant would either receive standard THR or withdraw from THR entirely. Participants who withdraw at this stage will not be replaced and follow-up data will not be collected.

At the discretion of the CI, participants may be withdrawn from randomised surgery and/or from follow-up data collection if it is felt in their best interest to do so. Prior to surgery, if other surgeons have an opinion that participants need to be withdrawn from randomised surgery this would need to be discussed with the CI prior to the CI making a final decision on withdrawal.

For randomised participants, all data collected up to the point of change in their participation status or withdrawal will be retained and used in the analysis. Participants who withdraw before randomisation will not be included in the final analysis. If the THR was not performed as scheduled

for unexpected reasons such as bed shortages, industrial action, staffing issues, participant short term medical issues (e.g. acute respiratory or urinary infections just prior to surgery) etc then the participant's' surgery would be rescheduled to the next available appropriate time as close as possible to the original surgical date.

For individuals who have provided informed consent, but who later lose capacity during the trial the following process will apply; the consent obtained prior to loss of capacity will not endure the loss. The participant will stop their participation but data already collected up to the point of loss of capacity will be retained and will be used in analysis.

6.8.1 Loss of contact with participant

If contact is lost with a participant at any point during the trial and they have not explicitly expressed a wish to end their trial participation, the site Research Team will try and establish contact. A minimum of three attempts to contact the participant should be made. If there have been several failed attempts at contacting the participant, it is acceptable to try and re-establish contact at the next follow-up time point. Participants as such can be described as "having lost contact for now".

If the site Research Team is successful in re-establishing contact with the participant, they must ask them to confirm if they wish to continue their participation in the trial. It may be at this point they wish to withdraw, or change their participation status (as detailed in section 6.8).

At the end of the trial, if any participant who lost contact with the trial without explicitly asking to stop participating and for whom no further data was obtained, they are to be described as having been "lost to follow-up".

6.9 Sample collection, transportation, analysis and storage

Obtaining blood samples will be coordinated by the site Research Team. Blood samples will be analysed for serum creatine kinase (CK), and C-reactive protein (CRP) biomarkers pre-operatively and post-operatively at day 0/1 and 6 weeks. The pre-operative samples will be obtained during the participant's routine surgical consenting clinic or pre-operative assessment. The post-operative samples will be obtained whilst the participant is still an inpatient. The 6-week post-operative samples will be obtained during the participants' routine 6-week post-operative surgical review appointment.

All samples will be handled and processed by the local laboratories at the Royal Devon & Exeter Hospital, adhering to all relevant Trust Standard Operating Procedures (SOP) and working instructions.

For participants having their surgery at the NGE, samples will be collected by the clinical staff and couriered back to the RDE for analysis via the routine courier service provided by the Trust.

Blood results will be transcribed from the participant's electronic record into the trial database by the site Research Team.

6.10 Co-enrolment

Any co-enrolment to other research studies will need to be approved by the CI and Co-CI, and the site Research Team.

6.11 End of trial

All participants will be actively followed up until their 12-month (52 week) follow-up and it is at this time point that the participant will complete their involvement in the trial. The end of the trial as a whole will be after all trial participants have completed all follow-ups i.e. when the last participant follow-up at 12 months (52 weeks) post-operative has been completed, no further follow-up is planned, all data queries have been resolved, the database locked, and the analysis completed and the results published. It is at this point that participants and their GP will be sent a notification of treatment allocation letter informing them of which THR technique the participant received.

A declaration of end of trial form will be submitted to the NHS REC who awarded favourable opinion within 90 days of the end of trial.

If the trial is terminated early, the trial will end on the date the Sponsor formally declares the trial terminated in writing. The main NHS REC will be notified of early termination within 15 days of the Sponsor deciding to end the trial.

7 SAFETY REPORTING

7.1 General definitions

Term	Definition
Adverse Event (AE)	Any unintentional, unfavourable clinical sign or symptom, or any new illness or disease or the deterioration of existing disease or illness.

Serious Adverse Event (SAE)	An SAE is considered to be any event that leads to
	• Death
	• Serious deterioration in the health of the participant that results in:
	  ○ life-threatening illness or injury;
	  ○ permanent impairment of a body structure or function;
	  ○ in-patient hospitalisation or prolongation of existing hospitalisation;
	  ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
	  ○ Chronic disease
	• Other important medical event.
	
	Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
	
	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Related and Unexpected SAE (RUSAE)	A related and unexpected SAE is an event that is related to the intervention, and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence.

7.2 Operational Definitions

The safety reporting flowchart in section 7.3.1 summarises the safety reporting process.

7.2.1 Adverse Events (AE)

AEs should be recorded from the point of surgery to the end of trial participation.

Not all non-serious AEs need to be recorded or reported, as described in the following sections.

7.2.2 Non-reportable adverse events

Some events which occur during treatment and recovery will be considered normal aspects of the anaesthetic and post-operative recovery process, and that occur frequently after surgery. They will not need reporting as AEs, unless in the opinion of the CI are untoward, excessive, or outside of what might normally be expected for the procedure, or fall into the category of an SAE. These include:

- Nausea and/or vomiting after surgery
- Drowsiness or headache after surgery
- Temporary low blood pressure after surgery
- Sore throat after surgery
- Itching after surgery
- Post-operative pain (note that this will be collected as an outcome) unless this is considered abnormal by the treating clinical team
- Memory loss or confusion during the hospital stay only, or which the treating clinician believes is due to analgesics
- Numbness on the lateral side of the surgical wound
- Early wound oozing which spontaneously resolves
- Bruising, unless this is considered abnormal by the treating clinical team
- Mild discomfort during or immediately after physiotherapy (inpatient and outpatient).

7.2.3 Reportable adverse events

Some events will be considered reportable expected AEs (or SAEs, if they meet the criteria). In certain cases, the diagnoses will be confirmed, where there is uncertainty, by the treating clinician. These include:

Those related in general to surgery and anaesthetic (within 6 weeks of surgery):

- Urinary retention
- Chest infection
- Myocardial infarction
- Stroke
- Nerve or vessel injury due to local anaesthetic (i.e. local blocks or spinal anaesthetic)
- Spinal haematoma.

Those related to the operation itself (within 12 weeks of surgery):

- Infection
- Wound healing problems
- Fracture of the bone around the hip replacement
- Implant failure, dislocation, or loosening
- Revision surgery or other corrective surgery
- Thrombosis (deep vein thrombosis, pulmonary embolus, cerebral infarct)
- Damage to nerves or vessels in the surgical area
- Persistent muscle soreness or muscle injury
- Bruising
- Haematoma

7.2.4 Causality

Causality of reportable SAEs will be assessed by the CI (in their role as site PI) or authorised delegate), see table 2. All SAEs which are possibly, probably or definitely related to the intervention will be categorised as 'related'. If the CI or delegate is unable to assign causality within 24 hours of the site becoming aware of the event, the SAE will be treated cautiously and subjected to expedited reporting (see section 7.3 below).

Table 2: The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the site PI (or delegate) using these descriptions:

Relationship to trial procedure	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment)
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments)
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

7.3 Reporting adverse events

All reportable AEs/SAEs/RUSAEs should be recorded from the point of surgery to the end of trial participation at 12 months (52 weeks) follow-up post-operatively.

SAEs must be reported directly onto REDCap **within 24 hours** of the blinded site Research Team becoming aware of the event. SAEs classed as possibly, probably or definitely related AND unexpected (RUSAEs) will be reported by ExeCTU to the Sponsor within 24 hours of ExeCTU staff becoming aware. The Sponsor is responsible for onward reporting of RUSAEs to the REC within 15 days of the event being reported to ExeCTU in REDCap. However, if the event results in death the SAE will be reported to the REC within 7 days of the event being reported to ExeCTU in REDCap.

The CI (in their role as site PI) or their delegate, is responsible for signing off reportable SAEs within the EDC system. This will be a role restricted task that only authorised users of the EDC can complete.

For each SAE the following information will be collected:

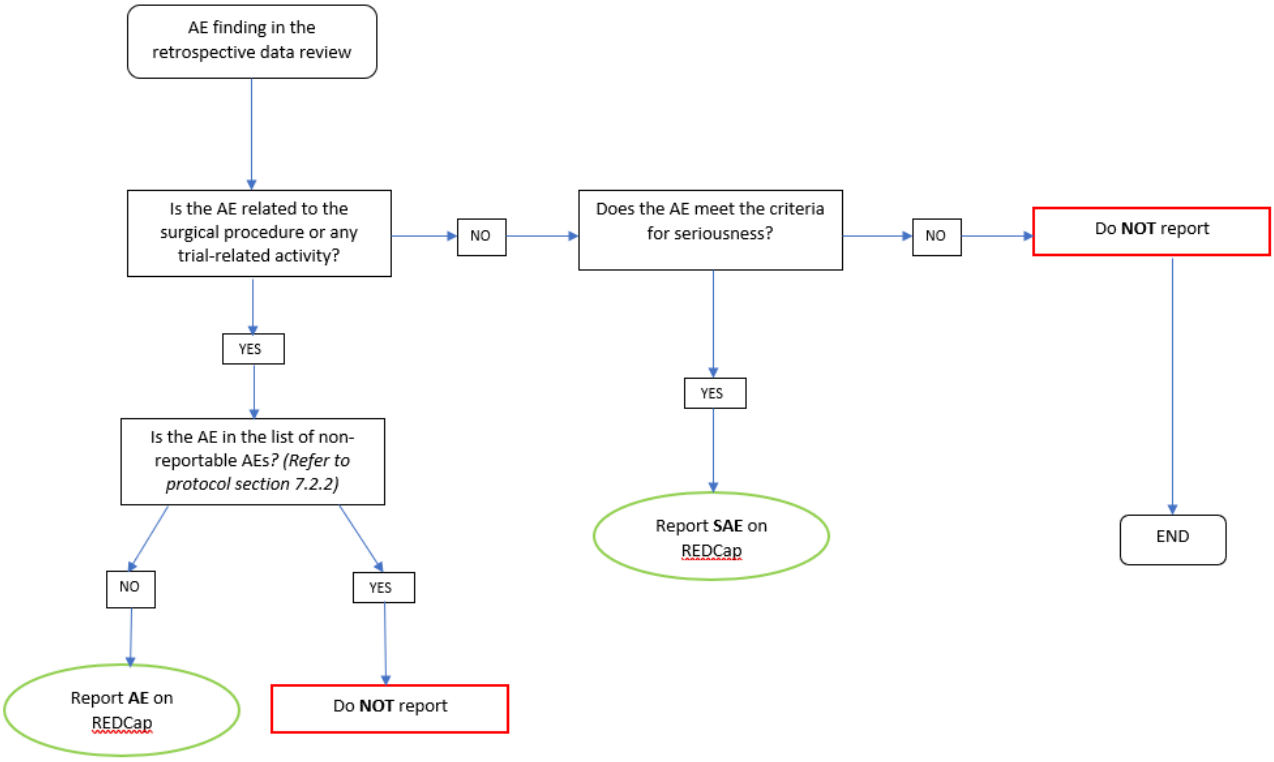
- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention)

Any change of condition or other follow-up information should be updated directly onto REDCap as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. An outcome of 'unknown' is not considered to be an acceptable final outcome. An outcome of 'not yet resolved' is an acceptable final outcome for non-serious AEs at the end of a participant's involvement in a trial, and for SAEs at database lock.

Where SAE causality is initially assessed by an authorised delegate of the CI but not the CI themselves, the CI (in their role as CI, as opposed to site PI) will record a second assessment of causal relationship. The CI may upgrade the causality assessment (e.g. from not related to related) but may not downgrade the assessment (e.g. related to not related). Where a causal relationship is suggested, the CI will record an assessment of expectedness.

The TSC and DMC will periodically review SAE data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

7.3.1 Safety reporting flowchart (figure 2)



7.4 Notification of deaths

All deaths occurring after randomisation until the 12-month post-operative time point, or participant withdrawal from the study, irrespective of their relationship to the trial treatment, should be reported to ExeCTU via REDCap as an SAE within 24 hours of identifying the death. In addition, if the CI becomes aware of a participant death outside this period, that appears to be related to the study intervention, this should also be reported as an RUSAE.

8 STATISTICS AND DATA ANALYSIS

8.1 Proposed sample size

The Research Team completed a pilot trial of elective THR patients, from the same population as the proposed trial population. The mean OARS score at 6 weeks post-operatively was 72.4 (N=126) in the source publication [28], compared with 72.9 in the pilot sample (N=17; 6 PSPA, 11 SPAIRE). The source publication included a combination of participants receiving hip and knee surgery; however, it is thought that OARS scores will be comparable in these groups. Whilst the mean scores were similar in the pilot sample and source publication, the standard deviation (SD) for the pilot data was higher at 24.9 compared with 17.5, which is likely due to the smaller sample size of the pilot trial. Therefore, the SD from the source publication was used to inform the sample size, with the upper bound of a one-sided 80% confidence interval (18.5) used in the calculation.

The OARS is a newly published early outcome score that currently has limited data available, and no other publications beyond the original score paper [28]. The OARS group have not yet published data regarding the Minimal Important Difference (MID, also reported as MCID – Minimal Clinical Important Difference), which is often used as the target difference for comparisons between groups.

Published data relating to the well-validated and widely used OHS by the same Oxford group, which is on a scale of 0-48, worst to best, was used to inform our figures for a reasonable MID for the OARS [33]. Although this is not ideal, this was the closest reasonable comparator available. The OHS has a corresponding MIC for an individual patient of 7.5 points and an MID of 5 points (for between-group comparisons) on the 0-48 scale [34]. Scaling up the OHS MID of 5 points to be in line with the 0-100 scale for the OARS, results in a scaled MID of 10 points, which we considered appropriate to use as a conservative target difference for sample size estimation based on OARS as the primary outcome.

To achieve 90% power to reject the null hypothesis of equal means when the population mean difference is 10 points with SD of 18.5 and with a two-sided significance level (alpha) of 0.025 (two comparisons: PSPA vs PA; SPAIRE vs PA), a total of 87 participants per treatment group is required. Allowing for a 15% drop out rate, this becomes 103 per group (309 in total).

Having had the opportunity to review means and SDs for the primary outcome across treatment groups at an interim period during trial conduct (including data from 187 participants), it was noted that the observed SDs were higher than the SD used to inform the original sample size calculation (18.5). Based on observed SDs across treatment groups, a revised sample size of 321 participants was determined. (To maintain blinding, the observed SDs used to inform the revised sample size are not presented here, but are recorded in an unblinded area of the Trial Master File.) It was also noted that completion rate of the primary outcome was approximately 95%, well in excess of the 85% completion rate assumed in the original sample size calculation. Hence, accounting for 5% loss to follow-up the revised recruitment target is 339 participants (an increase of 30 participants, or 10% of the original recruitment target). This increased sample size was recommended by the DMC in their meeting on 03 February 2025 and endorsed by the TSC in their meeting on 10 February 2025. NIHR then approved the amendment to increase the sample size accordingly.

8.2 Planned recruitment rate

The RDE completes approximately 800 THR procedures each year, and approximately 400 per year would be eligible for recruitment to this trial. Therefore, over the planned 2-year recruitment period, we will recruit the required sample size (339 participants) from a population of approximately 800 eligible patients. The trial will be supported by a Research Coordinator based at the Hip Unit of the RDE to assist the clinical team with recruitment activities. Eligible patients will be identified prior to pre-operative assessment and contacted via phone. Those interested in taking

part in the trial will be sent patient information leaflets. Patients will give informed consent to the trained research coordinator during their routine pre-operative assessment.

Two previous THR single-centre studies at the RDE of the same patient population using the same MAKO system have achieved a recruitment rate of approximately 71%, (i.e. 56 patients were approached to achieve the recruitment target of 40 participants). However, these were cohort studies, and as such did not require participants to attend additional research follow-up appointments, which was likely to increase the recruitment rate compared with studies involving additional follow-up. An ongoing RCT within the Knee Unit of the RDE, also using MAKO robotic-assistance, requires participants to attend five additional in-person follow-up appointments compared with standard care. This trial is currently achieving a recruitment rate of approximately 50%, i.e. 50% of eligible patients have agreed to take part in the trial. Therefore, in the proposed trial with a requirement for two additional remote patient follow-up periods, and the support of a research coordinator to assist with recruitment activities, we believe it is reasonable that we will achieve a recruitment rate of 50-70% for the proposed trial. Whilst this is higher than the recruitment rate of many NIHR-funded surgical RCTs, based on current studies being completed within the hip and knee units of the RDE, we believe this is an achievable recruitment rate.

Based on the eligible patient cohort of approximately 400 per year (800 over the 2-year recruitment period), the minimum recruitment rate to achieve full recruitment of 309 patients within 24 months is 39% (i.e. all 800 patients contacted in order to recruit 309). This provides an acceptable margin, such that full recruitment can still be achieved, even if the recruitment rate is below that anticipated, or if hospital capacity is reduced compared with previous years.

This recruitment target includes a 15% drop-out to ensure that the trial will still have the required power, and previous and current recruitment rates in both the RDE Hip and Knee Units have been used to estimate that the recruitment rate is achievable within the allocated time period. There are no competing studies for recruitment of the patient population.

Following revision of the recruitment target to 339 participants, it is anticipated that full recruitment will be achieved within the same timeframe as for the original recruitment target of 309 participants, due to the successful recruitment into the trial, exceeding the initial anticipated recruitment rate. It is noted that the anticipated non-completion of the primary outcome has been revised to 5%, reduced from the original 15%.

8.3 Participant flow through the trial

Participant flow through the trial, from initial screening to final 52-week follow-up, will be reported according to CONSORT guidelines [35].

8.4 Statistical analysis plan

A detailed statistical analysis plan will be developed during the recruitment phase of the trial, and will be approved by the Trial Steering Committee (TSC) prior to database lock. Following approval, any amendments to the SAP will be documented, with date and nature of amendment, and reason for amendment. Amendments to the SAP will be discussed with the TMG and TSC.

The primary analyses and selected sensitivity analyses will be performed by a statistician who is blinded to intervention allocation. These analyses will be performed following final data cleaning and database lock. Following unblinding of the trial team, after presentation of the primary analyses and consideration of the results of the trial, the remaining sensitivity analyses will be performed.

Participant characteristics at baseline will be presented descriptively within and across the three treatment groups. Continuous outcomes will be reported as the mean and standard deviation, plus

the median and either minimum/maximum or interquartile range. Categorical and binary variables will be reported as percentages. All outcomes will be reported descriptively using data for all follow-up times where reported. Demographic characteristics of participants who do not provide 6-week follow-up data (OARS) will also be presented, for comparison with characteristics of participants included in the primary analysis.

8.5 Primary outcome analysis

8.5.1 General principles

The primary outcome, OARS measured at 6-week follow-up, will be analysed using linear regression modelling with adjustment for minimisation factors (it is noted that OARS is not reported at baseline as it would not be appropriate to do so). For each of the two pairwise comparisons with PA, i.e. PSPA vs PA and SPAIRE vs PA, the between-group mean difference will be reported with a two-sided 95% confidence and p-value. To take into account the fact that there are two comparisons of interest, the threshold for significance for the primary outcome will be 0.025 (two-sided); this approach is consistent with the approach taken for the sample size calculation, although confidence intervals will be at the 95% level. In addition, a global p-value comparing means across all three treatment groups will be reported, plus the mean difference for SPAIRE vs PSPA and the associated two-sided 95% confidence interval.

8.5.2 Estimands framework

To fit with the estimands framework, a treatment policy approach will be used to deal with intercurrent events that relate to receipt of treatment, e.g. receipt of THR not as allocated, or failure to receive THR (for those outcomes that are valid in absence of THR). Deaths during the trial will be handled using the 'while alive' approach; participant data collected prior to death will be included in the analyses. In the event of death prior to 6-week follow-up, the outcome data will be deemed as 'non-existent' and will not be imputed.

As a sensitivity analysis, a principal stratum approach will be used, repeating the analysis including only those participants who received THR as allocated; these participants will be considered as 'always compliers' i.e. they will always receive treatment as allocated.

8.5.3 Approach to handling missing data

Missing outcome data (i.e. where the participant is not known to be deceased prior to the point of data collection) will be considered as 'missing at random'. It is also noted that OARS, OACS and SAPS are not valid outcomes for participants who do not receive THR, so will not be imputed for such participants. A multiple imputation approach will be used to impute missing outcome data. Imputation algorithms will include treatment group, minimisation variables, baseline scores (where available) for any unbalanced baseline characteristics thought to be predictive of outcome, and baseline characteristics found to be predictive of a missing primary outcome at 6-week follow-up. A sensitivity analysis will then be performed using the methods described in Sections 8.4.1 and 8.4.2 above, including both observed and imputed data, for both the treatment policy analysis and the principal stratum analysis.

8.5.4 Sensitivity analyses

Baseline descriptive data will be scrutinised for balance across the three treatment groups. Should any participant characteristics be considered unbalanced, and thought to be predictive of outcome, sensitivity analyses will be performed to adjust for these characteristics, using the methods described above.

Further sensitivity analyses will account for clustering by surgeon, by using a mixed model with a random effect on surgeon, in addition to adjustment for minimisation factors.

8.6 Analyses of secondary outcomes

8.6.1 General principles

For the secondary outcomes, the threshold for significance will be (two-sided) 0.025, and a global p-value comparing effects across all three treatment arms will be reported in addition to two-sided 95% CIs for all three pairwise comparisons; no corrections will be made for multiple testing, but p-values will be interpreted in the light of the number of comparisons being made.

Continuous PROM outcomes (OACS, SAPS, OHS, LEFS, EQ-5D-5L) will be analysed using the same principles as for OARS; OHS, LEFS and EQ-5D-5L will be collected at baseline, so baseline scores will be adjusted for. In addition, the four physical activity outcomes, the two sleep outcomes and the biomarkers, CK and CRP, will be analysed using these principles.

Time to discharge from hospital is to be measured in terms of the number of nights spent in hospital. It is anticipated that he majority of participants will be discharged on the day of surgery, so the number of nights spent in hospital will be 0. The number of nights spent in hospital will be reported descriptively by participant group, and also analysed using a negative binomial model, which will account for zero-inflation, with adjustment for minimisation variables.

Analgesia outcomes will be modelled using appropriate methods (i.e. linear regression modelling for dose outcomes and logistic regression modelling for binary outcomes).

Deaths will be reported descriptively, by allocated group, for the full period of the trial from randomisation to 12-month follow-up, and for the following time periods:

- Post-randomisation and pre-operative
- Peri-operative (within 24 hours of surgery)
- 1 day to 6 weeks post-operative
- More than 6 weeks to 52 weeks post-operative

Furthermore, the odds ratio for death (at any time during follow-up to 52 weeks post-operative) comparing PSPA vs PA, SPAIRE vs PA, and SPAIRE vs PSPA will be reported with two-sided 95% confidence intervals.

8.6.2 Estimands framework for secondary outcomes

For all secondary outcomes other than death, the same estimands framework will apply; if death occurs prior to any follow-up time, the outcome data that would have been collected will be deemed as non-existent data.

For death as an outcome, the treatment policy and principal stratum approaches will be used.

8.6.3 Approach to handling missing data for secondary outcomes

For all PROM secondary outcomes, physical activity secondary outcomes, sleep secondary outcomes, CK and CRP, multiple imputation across time points of data collection will be performed. Sensitivity analyses including observed and imputed data will be performed according to the estimands framework and general principles described above.

It is assumed that there will be no missing data for blood loss during surgery, duration of surgery, and length of hospital stay.

8.6.4 Sensitivity analyses for secondary outcomes

Sensitivity analyses with adjustment for unbalanced baseline characteristics, and using a mixed model with random effect on surgeon, will be performed for all continuous secondary outcomes, and for the number of nights in hospital.

8.6.5 Supplementary analyses

For all continuous secondary outcomes collected at more than one post-randomisation time point, a mixed model will be performed with a random effect on participant, including data collected at all time points. The interaction between treatment and time points will be reported with a two-sided 95% confidence interval and global p-value. These models will be performed for the treatment policy and principal stratum approaches.

8.7 Other analyses

No subgroup analyses are planned.

8.8 Interim analyses

No interim analyses are planned.

8.9 Adverse events analyses

SAEs will be reported descriptively by treatment as received (with footnotes to indicate where treatment received was not as allocated).

8.10 Mediation analyses

The potential for mediation effects of allocated treatment on OARS at 6-week follow-up, via an inflammatory effect measured by CRP and CK at day 0/1 follow-up, will be investigated using causal mediation modelling, using observed data only.

8.11 Other statistical considerations

Any amendments to the statistical analysis plan following initial approval by the TSC and sign-off by the senior statisticians and CI will be documented.

9 DATA MANAGEMENT

The handling, and storage of all personal data collected during the trial will comply with the Data Protection Act 2018 and the General Data Protection Regulation.

9.1 Data collection tools and source document identification

The primary data sources will be the participant's electronic medical notes on EPIC and trial-specific electronic Case Report Forms (eCRFs). Data will be collected contemporaneously through the trial on eCRFs with information extracted from source data within the participant's clinical records. PROMs data will be recorded pre-operatively, and at 6 weeks, 6 months (26 weeks) and 12 months (52 weeks) post-operatively with direct participant input onto REDCap. This is with the exception of paper PROMs should the participant opt for this, and the site Research Team will

transcribe the PROMs data onto REDCap once received from the participant. Results from blood biomarker collection pre-operatively and at 6 weeks post-operatively will be obtained from participant medical notes on EPIC and transcribed by a member of the site Research Team onto REDCap. Physical activity monitoring data will be uploaded and stored locally, and transferred pseudonymously to members of the University of Exeter Research Team (Co-CI) for processing.

Participants will be identified by a trial number allocated at the point of enrolment which will ensure anonymity of data recorded electronically. This will be the same as their randomisation number, however different from their participant screening number.

Sites will be required to answer data queries raised by ExeCTU within a timely manner within the trial database. A data cleaning work instruction will be provided to sites.

A separate Electronic Data Capture (EDC) project will be used to store personal identifiable data (i.e. names, addresses, email addresses, telephone numbers) that will be separate from the research data. Personal data will be collected to facilitate the sharing of newsletters and trial results and assist with retention and follow-up activities. Access to the contact details will be restricted to individuals authorised by the CI. All EDC system users will require individual log-in credentials and authorisation from an approved member of the trial management team before access is granted. The EDC system will incorporate role restriction such that individual users will only be able to access and enter or edit data as their individual permissions allow. The ExeCTU trial management team will run regular reports for missing data and remind sites at least monthly to enter data that is expected and document any reasons for missing data.

9.2 Data handling and record keeping

A Data Management Plan (DMP) will be drafted prior to starting participant recruitment and will be updated throughout the trial as appropriate. Working instructions will be provided to the RDE site on record keeping and data entry processes. Electronic systems will be validated, tested and documented before starting recruitment. The DMP and validation documents will be available upon request to ExeCTU.

9.3 Surgical data and robotic-assisted surgery session files

Legal agreements are in place between Stryker and the RDUH to protect participants' identity and personal information will be held confidentially in accordance with GDPR. These protections will remain even if data is transferred outside the EU, such as to the USA. Stryker will hold data from previously received CT scans for the purposes of planning the surgery, and could potentially use it for linkage of with the session files and surgery data. However, there will be strict contracts in place to ensure data confidentiality is maintained. This data sharing has already been approved by RDE Governance and is already currently occurring for patients undergoing MAKO THRs as part of routine clinical practice.

9.4 Data collection processes

The pre-, peri-, and post-operative data collection will be completed by members of the site Research Team. Surgical parameters and results of blood biomarkers will be collected from participant medical notes via EPIC, which constitutes source data, and PROMs data will be completed directly onto the REDCap database by the participant.

Physical activity monitoring data will be collected by members of the site Research Team with additional support provided by the Trial Manager and the Co-CI. Activity monitoring data will be uploaded and stored locally, and transferred pseudonymously to members of the University of

Exeter Research Team (Co-CI) for processing. The Co-CI has led previous trials using ActivInsights activity monitors at the RDE, and will process the activity data to collect the specific activity outcome measures that will be used in this trial. These outcomes will be securely transferred to ExeCTU to store on the same secure database as all other outcome measures.

9.5 Data access

Access to data held at the participating site will be restricted to those holding a substantive or honorary contract for the RDE and who have a relevant purpose to access the data. Access will be granted to authorised representatives from the RDUH NHS Foundation Trust as the Sponsor, as well as representatives from the UoE for the purposes of auditing and monitoring the trial.

Participants will be asked to consent to representatives of the Sponsor or the UoE accessing their data that is relevant to their participation in the trial.

Data entered into the EDC system will be accessed by authorised members of the trial team at the participating site and at ExeCTU. Access will be restricted with individual log-in credentials, and site and role restriction applied so that individuals can only access data appropriate to their location and role.

9.6 Data shared with third parties

De-identified data that underlie the results reported in the trial will be deposited in the University of Exeter's Open Research repository and available for non-commercial use, on a controlled access basis, subject to suitable data requests and data sharing agreements. Data may be used for commercial purposes, according to the conditions above, but will need specific agreements in place prior to access being agreed. This may include a license fee.

9.7 Archiving

The Sponsor is responsible for arranging appropriate archiving on conclusion of the trial of the TMF and EDC system data. The RDE will be responsible for archiving their investigator site file, including paper consent forms and any paper PROMs, following the local NHS Trust archiving procedure.

Trial documentation and data will be archived for at least 10 years following the completion of the trial, as per local NHS Trust SOP.

10 MONITORING, AUDIT AND INSPECTION

A detailed monitoring plan will be agreed between the CI and Co-CI, ExeCTU and the Sponsor. The monitoring plan will be based on the risk assessment that will be reviewed periodically and in response to amendments to the trial protocol.

Monitoring will be conducted by a combination of remote and central monitoring led by ExeCTU. On-site monitoring will be conducted if one or more triggers are met, as detailed in the monitoring plan, or if concerns are raised by an individual with knowledge of the trial. The RDE will be expected to cooperate with remote and onsite monitoring procedures by provision of copies of requested documents in a timely manner and the completion of self-audit checklists. In the case of triggered on-site monitoring visits, the RDE will be expected to provide space for the monitor(s) to work on the NHS Trust premises and provide access to all documents requested in the notification of monitoring visit letter. The CI or delegated member of the site Research Team must be available during on-site monitoring visits. ExeCTU will provide the RDE with sufficient notice to prepare for a

monitoring visit. The Sponsor and/or regulatory authorities may audit or inspect any aspect of the trial, including ongoing site visits, at any time during the trial.

The DMC will review data completeness, data quality and accumulating safety data at agreed intervals throughout the trial.

11 ETHICS AND REGULATORY APPROVALS

11.1 Research Ethics Committee (REC) review and reports

The research will be performed subject to favourable opinion from a UK NHS REC and HRA, and local site capacity and capability confirmation from the Research and Development department. Ethics review of the protocol for the trial and other trial-related essential documents (e.g. PIS and consent form) will be carried out by an NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. All data will be stored securely, and will be stored in accordance with current legislation. The trial will be registered with ISCRTN before the first participant is recruited.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and trial Sponsor will be notified of the end of the trial (whether the trial ends at the planned time or prematurely).

The CI will submit a final report to the REC and HRA with the trial results, including any publications, within one year of the end of the trial.

11.2 Risks and benefits to trial participants

The eligibility criteria ensure that all trial participants require, and would normally have, one of the three trial options (SPAIRE, PSPA or PA) as routine treatment for their THR. Participants will also undergo pre-operative X-ray and CT imaging and post-operative X-ray imaging as part of their routine care. In general, therefore, the trial will not expose participants to risks additional to standard of care.

11.3 Public and patient involvement and engagement (PPIE)

The Exeter Hip Unit established a PPIE group during the development of this trial proposal, which included both patients and carers. Potential outcomes measures for the trial were explored by the Research Team through a PPIE workshop, facilitated by the Public Involvement team of the South-West Research Design Service, to explore patient and carer experiences of THR. The PPIE group was introduced to the overall research objective: to understand whether tendon-sparing approaches might improve the patient experience of THR. Outcome measures, including PROMs, performance outcome measures, and functional outcome measures, were discussed to identify the most suitable primary and secondary endpoints with which to assess the efficacy of the PSPA and SPAIRE approach compared with the standard PA.

Based on the feedback from the PPIE group, several outcome measures were identified for potential inclusion, in addition to the outcome measures collected as part of routine care:

- Hip abduction strength
- Hip external rotation strength
- Walking step rate and bout length

- Sleep quality
- Lower extremity function scale PROM

This PPIE workshop, combined with pilot studies and additional PPIE consultation, led to the identification of the OARS PROM as a suitable primary outcome measure, and secondary outcome measures that will provide additional measures of efficacy of the PSPA and SPAIRE approach compared with the PA.

Several attendees of the PPIE workshop were also recruited to provide feedback on the trial proposal lay summary, and have agreed to provide similar feedback on Patient Information Sheets during the trial.

Further involvement and engagement will be completed during the trial. When patients are enrolled into the trial, they will be asked whether they would like to be kept informed about developments of the trial, and whether they would be interested in attending PPIE events. This will allow the Research Team to send trial updates via an email newsletter (or by post when requested), and ensure that participants have the opportunity to attend engagement events at least once a year.

PPIE will also occur throughout the trial through membership of the TMG, and the TSC.

11.4 Regulatory compliance

Recruitment will commence at site once the RDE Research and Development department has confirmed capacity and capability to deliver the trial.

The latest HRA guidance will be followed at all times with regard to notification and implementation of amendments at sites.

11.5 Protocol compliance

All staff undertaking research activities outlined in the protocol will be trained prior to commencing work on the trial. The eCRFs and EDC system will be designed to assist in adherence to the protocol by guiding trial personnel through the assessments and data collection. The EDC system will also be validated to minimise protocol deviations. The site Research Team will be trained to notify the Trial Manager in the event of a protocol deviation or suspected or actual serious breach, by reporting directly to ExeCTU through REDCap. A deviation log will be maintained in REDCap by ExeCTU and reviewed regularly by the CI, Co-CI and the Sponsor. Recurrent deviations will be discussed with the TMG and TSC, as appropriate. The Trial Manager will work with the site Research Team to identify the cause of the deviations and put in place steps to mitigate them, as appropriate. Protocol compliance will be reported at the end of the trial.

11.5.1 Notification of serious breaches to GCP and/or the protocol

A serious breach is a breach that is likely to affect:

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

All suspected serious breaches will be notified to the Sponsor by a member of the ExeCTU trial team within 24 hours of becoming aware of the breach, in accordance with the ExeCTU SOP. The RDE site will notify ExeCTU of the suspected serious breach in the first instance by reporting directly onto REDCap. The suspected breach will be logged on the ExeCTU Quality Management System (QMS). The Sponsor representative will decide if the event constitutes a serious breach, and if so will report to the REC **within 7 days** of becoming aware as per the REC SOP. In the event of a serious breach, the Sponsor, ExeCTU and the individuals involved will work together to

agree and implement a Corrective and Preventative Action (CAPA) plan and follow up on the plan at agreed intervals to ensure effective implementation.

11.6 Conflicts of interest

There are no competing interests associated with this trial. The trial is aiming to identify whether tendon-sparing approaches for THR lead to better patient outcomes, but there is no intellectual property associated with the approaches used in the trial.

Members of the surgical team (Mr Al-Amin Kassam, Mr Jonathan Howell, Mr Matthew Wilson, Mr Matthew Hubble, Mr John Charity and Prof John Timperley) do have commercial ties with Stryker, who manufacture and distribute the THR devices and MAKO robotic guidance system that will be used in the trial. However, all surgical interventions used in the trial will adopt the same medical devices and surgical guidance system, and no member of the surgical team will be involved in the collection or analysis of outcome measures at any time point, and therefore, will not have any influence over the evaluation or reporting of trial results.

11.7 Indemnity

This is an NHS-sponsored research trial. If an individual suffers negligent harm as a result of participating in the trial, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim. Any harm to participants arising from the design or management of the research is covered by the NHS Litigation Authority. There are no arrangements for the Sponsor to pay compensation in the event of harm to research participants where no legal liability arises.

11.8 Amendments

All substantial amendments and relevant non-substantial amendments will be discussed by the TMG. The CI, Co-CI and Sponsor will be responsible for the final decision on making an amendment to the protocol. The approval of all TSC members will be sought for substantial amendments to the protocol in advance of submitting them to the REC and/or HRA, and if necessary, a meeting of the TSC will be convened to discuss the amendment. Approval will also be sought from the Funder for all substantial amendments, and the Funder representative will be notified of relevant substantial amendments in advance of submission. A full list of all substantial and non-substantial amendments will be provided as part of regular funder reports.

The Sponsor will decide if an amendment is substantial or non-substantial following HRA guidance. All amendments will be submitted to the NHS REC that issued a favourable opinion (if appropriate) and the HRA following the appropriate HRA amendment process in place at the time of submission. Amendments will be communicated by the Trial Manager to the Research and Development department and site Research Team at the RDE site as soon as possible upon receipt of approval to do so from the HRA.

A Co-CI or delegate will inform the trial registry of changes to the trial.

An amendment log will be maintained by the Trial Manager and filed in the TMF. The protocol version history will be recorded in an appendix to the protocol. The RDE site will be provided with an updated document version control list where applicable following an amendment.

12 DISSEMINATION, OUTPUTS AND ANTICIPATED IMPACT

12.1 Dissemination

The results of this trial will be shared with academic, clinical, patient, and public audiences. Participants will receive a plain English summary of the trial results, if they have indicated this on their consent form, and this will be via post or email according to their preference.

The Research Team will disseminate the results of the trial through leading academic journals in their field, and will engage with academic and clinical communities through academic conferences and specialist hip meetings. The results will be posted on the publicly available registry (ISRCTN).

The clinical team in the Exeter Hip Unit of the RDUH lead multiple hip training courses worldwide, which are attended by hundreds of surgeons each year. These courses, along with the established Exeter Hip Fellowship programme will be used to share the results of the trial, and should it be successful, will provide training opportunities relating to the surgical approaches that are shown to be most beneficial to patients. This may additionally include the production of a video of the different surgical approaches to assist with surgical training.

PPIE events and initiatives will be held regularly throughout the project. When patients are enrolled into the trial, they will be asked whether they would like to be kept informed about developments of the trial, and whether they would be interested in attending PPIE events. This will allow the Research Team to send trial updates to interested participants via an email newsletter, and ensure that participants have the opportunity to attend engagement events that will take place at least once a year. The engagement events will also be used to provide trial updates, but will also focus include opportunities to co-develop materials, such as infographics, which will be shared with a wider audience through the Exeter Hip Unit website and social media channels. The PPIE lead, Ms Alison Smeatham, and Co-CI, Dr Timothy Holsgrove, will also investigate other PPIE opportunities based on the range of initiatives that they have previously been involved in, including public talks and science fairs, video lectures, animations, and image of research installations. Specifically, this may include the development of an animation of the different surgical approaches, along with a summary of the trial results aimed at a non-specialist audience.

12.2 Future adoption, implementation, and impact

If successful, it is anticipated that the results of this trial will provide the evidence necessary to plan a future multi-centre RCT to compare the best-performing tendon-sparing approach (PSPA or SPAIRE) identified in this efficacy trial with the gold standard PA, to assess whether the efficacy results are generalisable across the NHS. If only one of the experimental groups (PSPA or SPAIRE) is found to be superior to PA, that one will be taken forward as the intervention for the future trial. If both SPAIRE and PSPA are found to be superior to PA, then it is anticipated that the tendon-sparing approach that will be taken forward will be selected based on the following criteria, if known: which is easier to implement; which is more cost-effective to implement; participant feedback; and the mean differences and confidence intervals for PSPA vs PA and SPAIRE vs PA. If the selection of a single tendon-sparing approach is not possible, it may be justifiable to propose a 3-arm multi-centre effectiveness RCT. This multi-centre RCT would align with the aims of the NIHR Health Technology Assessment (HTA) programme, and would be in collaboration with NHS sites that have the same robotic-guidance system as currently used at the RDE. This is currently a limited number (12 sites) but is likely to be substantially higher by the time such a trial could commence, as robotic-assisted surgery is rolled out across the NHS.

12.3 Intellectual property and commercialisation

This trial will investigate surgical approaches, and therefore will not lead to the development of intellectual property or commercialisation. Instead, if successful, the research will lead to the training resources outlined in the dissemination section above in order to maximise adoption, implementation, and impact.

13 REFERENCES

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018, Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet, 392(10159), pp. 1789-1858. https://dx.doi.org/10.1016/S0140-6736(18)32279-7.

[2] Arthritis Research UK, 2013, Oseoarthritis in General Practice. Arthritis Research UK, Chesterfield, UK. Available from: https://www.versusarthritis.org/media/2115/osteoarthritis-in-general-practice.pdf [Accessed 30/11/2021].

[3] National Joint Registry, 2020, 17th Annual Report 2020 - National Joint Registry for England, Wales, Northern Ireland and the Isle of Man - Surgical data to 31 December 2019. National Joint Registry, Hemel Hempstead, Herfordshire, UK.

[4] Kärrholm J et al, 2017, Swedish Hip Arthroplasty Register - Annual Report 2017. Swedish Hip Arthroplasty Register, Göteborg, Sweden.

[5] The New Zealand Joint Registry, 2018, Nineteen Year Report - January 1999 to December 2017. New Zealand Orthopaedic Association, Wellington, NZ.

[6] Blom AW et al, 2020, The effect of surgical approach in total hip replacement on outcomes: an analysis of 723,904 elective operations from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. BMC Med, 18(1), p. 242. https://dx.doi.org/10.1186/s12916-020-01672-0.

[7] Berry DJ, and Bozic KJ, 2010, Current practice patterns in primary hip and knee arthroplasty among members of the American Association of Hip and Knee Surgeons. J Arthroplasty, 25(6 Suppl), pp. 2-4. https://dx.doi.org/10.1016/j.arth.2010.04.033.

[8] Chechik O et al, 2013, Surgical approach and prosthesis fixation in hip arthroplasty world wide. Arch Orthop Trauma Surg, 133(11), pp. 1595-1600. https://dx.doi.org/10.1007/s00402-013-1828-0.

[9] Aggarwal VK et al, 2019, Surgical approach significantly affects the complication rates associated with total hip arthroplasty. Bone Joint J, 101-B(6), pp. 646-651. https://dx.doi.org/10.1302/0301-620X.101B6.BJJ-2018-1474.R1.

[10] Putananon C et al, 2018, Comparison of direct anterior, lateral, posterior and posterior-2 approaches in total hip arthroplasty: network meta-analysis. Eur J Orthop Surg Traumatol, 28(2), pp. 255-267. https://dx.doi.org/10.1007/s00590-017-2046-1.

[11] Wang T et al, 2019, Surgical injury and repair of hip external rotators in THA via posterior approach: a three-dimensional MRI-evident quantitative prospective study. BMC Musculoskelet Disord, 20(1), p. 22. https://dx.doi.org/10.1186/s12891-018-2367-1.

[12] Khan RJ et al, 2012, Magnetic resonance imaging features of preserved vs divided and repaired piriformis during total hip arthroplasty: a randomized controlled trial. J Arthroplasty, 27(4), pp. 551-558. https://dx.doi.org/10.1016/j.arth.2011.06.004.

[13] Tan BKL et al, 2019, Piriformis-Sparing Minimally Invasive Versus the Standard Posterior Approach for Total Hip Arthroplasty: A 10-Year Follow-Up of a Randomized Control Trial. J Arthroplasty, 34(2), pp. 319-326. https://dx.doi.org/10.1016/j.arth.2018.10.014.

[14] Borg H et al, 2009, External rotation strength deficit after hip resurfacing surgery. Disabil Rehabil, 31(11), pp. 865-870. https://dx.doi.org/10.1080/09638280802355387.

[15] Hakkinen A et al, 2010, Muscle strength and range of movement deficits 1 year after hip resurfacing surgery using posterior approach. Disabil Rehabil, 32(6), pp. 483-491. https://dx.doi.org/10.3109/09638280903171451.

[16] Stahelin T et al, 2002, Failure of reinserted short external rotator muscles after total hip arthroplasty. Journal of Arthroplasty, 17(5), pp. 604-607. https://dx.doi.org/10.1054/arth.2002.32187.

[17] Hanly RJ et al, 2017, The SPAIRE technique allows sparing of the piriformis and obturator internus in a modified posterior approach to the hip. Hip Int, 27(2), pp. 205-209. https://dx.doi.org/10.5301/hipint.5000490.

[18] Kim YS et al, 2008, Modified posterior approach to total hip arthroplasty to enhance joint stability. Clin Orthop Relat Res, 466(2), pp. 294-299. https://dx.doi.org/10.1007/s11999-007-0056-8.

[19] Domb BG et al, 2014, Comparison of robotic-assisted and conventional acetabular cup placement in THA: a matched-pair controlled study. Clin Orthop Relat Res, 472(1), pp. 329-336. https://dx.doi.org/10.1007/s11999-013-3253-7.

[20] Domb BG et al, 2015, Accuracy of Component Positioning in 1980 Total Hip Arthroplasties: A Comparative Analysis by Surgical Technique and Mode of Guidance. J Arthroplasty, 30(12), pp. 2208-2218. https://dx.doi.org/10.1016/j.arth.2015.06.059.

[21] Khan RJ et al, 2012, A comparison of a less invasive piriformis-sparing approach versus the standard posterior approach to the hip: A randomised controlled trial. J Bone Joint Surg Br, 94(1), pp. 43-50. https://dx.doi.org/10.1302/0301-620X.94B1.27001.

[22] Carpenter CVE et al, 2018, Validated repeatability of patient-reported outcome measures following primary total hip replacement: a mode of delivery comparison study with randomized sequencing. Acta Orthop, 89(6), pp. 628-633. https://dx.doi.org/10.1080/17453674.2018.1521183.

[23] Timperley AJ, 2018, The SPAIRE technique: Early outcomes and comparative data of the fisrt consecutive hip replacements. 19th EFORT Congress, Barcelona, Spain.

[24] Timperley J, 2018, The SPAIRE technique (Spare piriformis and internus, repair externus) for hip arthroplasty is safe and effective. Orthopaedic Proceedings, 100-B(SUPP_11), pp. 8-8. https://dx.doi.org/10.1302/1358-992x.2018.11.008.

[25] Binkley JM et al, 1999, The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. Phys Ther, 79(4), pp. 371-383.

[26] Wall BF et al, 2011, Radiation Risks from Medical X-ray Examinations as a Function of the Age and Sex of the Patient (HPA-CRCE-028). Didcot, UK. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/340147/HPA-CRCE-028_for_website.pdf [Accessed.

[27] Public Health England, 2020, Guidance Notes for Dental Practitioners on the Safe Use of X-ray Equipment 2nd Edition. London, UK. Available from: https://www.rqia.org.uk/RQIA/files/44/449bdd1c-ccb0-4322-b0df-616a0de88fe4.pdf [Accessed.

[28] Strickland LH et al, 2020, Development of a patient-reported outcome measure (PROM) and change measure for use in early recovery following hip or knee replacement. J Patient Rep Outcomes, 4(1), p. 91. https://dx.doi.org/10.1186/s41687-020-00262-1.

[29] Bergin PF et al, 2011, Comparison of minimally invasive direct anterior versus posterior total hip arthroplasty based on inflammation and muscle damage markers. J Bone Joint Surg Am, 93(15), pp. 1392-1398. https://dx.doi.org/10.2106/JBJS.J.00557.

[30] De Anta-Diaz B et al, 2016, No differences between direct anterior and lateral approach for primary total hip arthroplasty related to muscle damage or functional outcome. Int Orthop, 40(10), pp. 2025-2030. https://dx.doi.org/10.1007/s00264-015-3108-9.

[31] Dainty JR et al, 2021, Trajectories of pain and function in the first five years after total hip and knee arthroplasty : an analysis of patient reported outcome data from the National Joint Registry. Bone Joint J, 103-B(6), pp. 1111-1118. https://dx.doi.org/10.1302/0301-620X.103B6.BJJ-2020-1437.R1.

[32] Iflaifel M et al, 2022, Blinding of study statisticians in clinical trials: a qualitative study in UK clinical trials units. Trials, 23(1), p. 535. https://dx.doi.org/10.1186/s13063-022-06481-9.

[33] Beard DJ et al, 2015, Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. J Clin Epidemiol, 68(1), pp. 73-79. https://dx.doi.org/10.1016/j.jclinepi.2014.08.009.

[34] Yeo MGH et al, 2020, Are Oxford Hip Score and Western Ontario and McMaster Universities Osteoarthritis Index Useful Predictors of Clinical Meaningful Improvement and Satisfaction After Total Hip Arthroplasty? J Arthroplasty, 35(9), pp. 2458-2464. https://dx.doi.org/10.1016/j.arth.2020.04.034.

[35] Schulz KF et al, 2010, CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med, 8, p. 18. https://dx.doi.org/10.1186/1741-7015-8-18.