PROTOCOL

The Meniscal Transplant surgery or Optimised Rehabilitation full randomised trial (MeTeOR2)

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TRIAL SUMMARY

Summary of the trial is reported in table 1 below:

Table 1: Trial Summary

Trial Title	The Meniscal Transplant surgery or Optimised Rehabilitation full randomised trial (MeTEOR2).	
Internal ref. number (or short title)	MeTeOR2	
Trial Design	A multi-centre pragmatic, international, RCT of meniscal allograft transplantation compared to personalised knee therapy.	
Trial Participants	Adults with knee pain and/or functional limitation following meniscectomy but without large areas of articular cartilage loss or established OA.	
Planned sample size	144.	
Follow-up	Primary outcome: 24 months after randomisation. Secondary timepoints: 3, 6, 12, 18 and 24 months (with plans to apply for funding for 5 and 10 years*) post randomisation.	
Planned Trial Period	From: 1st June 2022 To: 30th November 2027 (note: long-term follow-up planned through to September 2035*).	
	Objectives	Outcomes
Primary	*Clinical Effectiveness*: To compare the clinical effectiveness of meniscus allograft transplant (MAT) or personalised knee therapy (PKT) at 24 months post randomisation. *Cost Effectiveness:* To assess the cost effectiveness of MAT compared to PKT from an NHS and Personal, Social Service (PSS) perspective.	Participant-reported knee function at 24 months, using the four-domain version of the Knee Injury and Osteoarthritis Outcome Score (KOOS4). Within-trial Incremental Cost-Effectiveness Ratio (ICER)

Secondary	To quantify and draw inferences on: Health utility, occupational status, sports participation, mental wellbeing, further surgery (treatment switching or secondary knee surgery), satisfaction with the outcome of treatment, participant global impression of change and adverse events at three (EQ5D-5L only), six, 12, 18 and 24 months after randomisation.	• KOOS4 at other time points. • Separate KOOS domains • International Knee Documentation Committee subjective score – baseline and 24 months only. • EQ-5D 5L • Short Warwick-Edinburgh Mental Wellbeing Scale • Tegner activity/sport scale • Work status • Satisfaction with the outcome of treatment. • Participant global impression of change. • Adverse events • Further knee surgery. • Resource use. • QALYs gained • Use of analgesics
Process Measure	To compare: number of days to initiation of treatment, rehabilitation attendance and participation expectation of outcome (baseline), in both groups. Alongside routinely collected data in screening logs, we will also collect the source of referral (as primary care/secondary care/participating site, and by geography) to assess referral patterns during the trial.	

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event

AE	Adverse Event

CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
IKDC	International Knee Documentation Committee
IMReF	International Meniscus Reconstruction Experts Forum
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
KOOS	Knee injury and Osteoarthritis Outcome Score
MAT	Meniscal Allograft Transplant
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
OA	Osteoarthritis
PI	Principal Investigator
PKT	Personalised Knee Therapy
PPI	Patient & Public Involvement
PSS	Personal, Social Service
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

1.1.1 What is the problem being addressed?

Pain and disability after meniscectomy can be a substantial lifelong problem. Every year, around 80,000 people in England undergo meniscectomy where part or all the meniscus is removed following a tear.(1) Some people have considerable and persistent pain after this and may have impairment of function and be unable to return to previous activities. The result is often many years of disability. There are few treatment options, especially when people are young (20s and 30s) because knee replacement at a young age is inadvisable.

Increasingly, surgeons are performing meniscal allograft transplants (MATs) to reduce pain and improve function in people with pain after meniscectomy.(2) After a meniscectomy, many people will, over time, develop osteoarthritis (OA). MAT may reduce this risk but there remains very little high-quality evidence to know if this is true.

MAT costs around £7,500 per case in the UK. It is a substantial cost burden for the NHS, although it is cheaper than some other technologies for comparable conditions (such as autologous chondrocyte implantation, recommended by NICE but costing twice as much).(3) It is an uncommon procedure (approximately 300 cases in 2019 in the UK, estimated NHS cost >£2M annually) but its use has increased greatly in recent years. The availability and usage of MAT varies widely around the UK, resulting in a potential inequity in access to treatment. This may be in part due to a lack of evidence about whether MAT or non-surgical care is more effective and whether it is cost-effective.

Given the high rates of meniscectomy and the proportion of people who have pain after meniscectomy (see below), it is likely that more people in the UK could benefit from MAT, if there was good evidence that it was effective.(1,4,5) At present, we have no comparative data to inform patients, surgeons, or NICE about whether MAT should be used or whether patients with this problem would be better treated with non-surgical means.(4)

1.1.2 Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

The meniscus is a c-shaped cartilage structure in the knee which distributes load between the joint surfaces. Tears are common, often from sporting injuries in young people. Most tears cannot be repaired, and the torn parts have to be removed with keyhole surgery; this is called an arthroscopic partial meniscectomy.

For the remainder of the protocol (unless stated otherwise), we will use the term meniscectomy to mean arthroscopic partial meniscectomy, which covers a spectrum from removal of a small piece of meniscus to almost all of it. A total meniscectomy involves removal of the whole meniscus, typically through an open approach, and is a historical procedure. Even a partial meniscectomy can render the meniscus ineffective, as the mechanical function of the meniscus may be disrupted, depending on the amount of meniscus removed.

Meniscectomy improves pain and other symptoms such as locking in the majority of people, but some have pain after surgery. People with pain after a meniscectomy can be very disabled and have access to few treatment options.

To illustrate the severity of pain and disability suffered by people with meniscal loss; in our pilot study baseline Knee Osteoarthritis Outcome Scores (KOOS4, range 0-100) for people being considered for MAT were similar to baseline KOOS4 scores in a trial of people awaiting knee replacement (MAT trial: mean KOOS4 47.4 (SD 16.5), mean age 28; TKR trial: mean KOOS4 48.0 (SD 12.4), mean age 66).(6,7) Poor pain and function scores at baseline have been reported in multiple large case-series of people undergoing MAT. Many of these people are in their late teens, twenties or thirties.(3,8) In our PPI interactions developing this study, patients have described substantial limitations and emotional distress as they adjust to disability at an age when they expect to be active, healthy and free of disability.

Ten years after arthroscopic meniscectomy, 20% of people have developed osteoarthritis (OA), increasing to 50% after 20 years.(4,9) If someone aged 30-39 has a partial meniscectomy, their risk of knee replacement after 15 years is 40 times that of the general population.(10) Knee replacements (KR) in young adults are prone to poor results, low levels of function and high failure rates. They are therefore usually avoided until a later age, meaning people often have to live with pain until they are at an age when KR might be considered reasonable, typically over 50.(11,12)

A MAT involves taking a donor meniscus from someone who has died. It can be stored frozen and then inserted into someone with a similar size knee. This is done mostly by keyhole surgery except for a small 2-3cm incision just below the knee, although for some people a small open incision may be used over the knee (typically around 7-8cm long). The choice between the two depends on the individual surgeon's technique.

Peak loading of the joint surfaces increases by 2.3 times after removing a meniscus. This is thought to cause pain, wear of the joint surfaces, and eventually knee OA.(13,14) In cadaveric testing, MAT has been found to restore peak joint loading to normal.(13,14) Restoring normal joint loading may reduce pain directly, and reduce future risk of OA. There is no direct evidence to prove this, and the pain relief observed in case series of MAT could be due to the rehabilitation that people receive. There are no surgical alternatives to MAT. Synthetic scaffolds are rarely suitable and have mixed results at best.(15)

Non-surgical management (rehabilitation) is also a viable option for people with pain after meniscectomy. A review in our unit (PROSPERO:122179) has found that pain and function improve over time after non-surgical care of meniscal tears.(16) If it were shown to be effective for persistent pain after meniscectomy, non-surgical rehabilitation would be safer, cheaper and does not reduce participation in work or other activities during the post-operative phase.

For people with pain and functional loss who have previously had meniscectomy, it is not known if the best decision is to offer the cheaper and potentially safer options of non-surgical rehabilitation, or if surgery in the form of MAT is needed to reduce joint loading and prevent ongoing pain and disability. No comparative studies exist (except our pilot) that allow us to determine which strategy is best.(4,17)

1.2 Existing knowledge and the need for the study

Our 2019 systematic review found 19 studies (N=1731 cases); 18 case-series of MAT and just one randomised study (our pilot).(4) Patient reported outcomes improved from baseline across all studies. However, there were no data on non-surgical management for people who had pain after meniscectomy. It was impossible to identify a viable comparison

group for MAT from the literature. The lack of a valid comparator is not something that could be resolved with a simple observational study; without randomisation, selection bias in any cohort study of meniscectomy would be too great. We have updated our previous review of MAT as part of the SCORE evidence synthesis (NIHR HTA: NIHR127398 - The clinical effectiveness and cost effectiveness of surgery for early osteoarthritis of the hip and knee joint) and have found no new evidence that answers the questions we address in this bid.

Long-term safety data exist on MAT. The technique and its indications are now well established.(2) In our review, case-series of MAT reported good graft survival at five years (above 80%) but lower survival at 10 years (typically 60-75%).(4) Many of these were in people with OA. MAT is now rarely used for OA.(4). Our 2019 case series of MAT performed in Coventry (N=240), found 95% and 80% graft survival at five and ten years respectively in people who did not have OA.(8). A third of people have some sort of further surgery, the majority being minor arthroscopy for removal of uncomfortable knots.(4,8) Otherwise, adverse events (thrombo-embolism, infection) are uncommon.

Non-surgical treatments (rehabilitation) do not expose people to the risks of surgery or the painful recovery period and in the short-term are much cheaper for the NHS. For early knee OA, there is strong evidence of benefit for non-surgical treatments; these include exercises, weight loss, lifestyle and activity advice, adjuncts such as orthoses and offloading braces, and NSAIDs when necessary.(18-21) There are no data on conservative care for people with pain after meniscectomy, but the principles of care for early OA apply to this population and it is reasonable to think they would have a similar beneficial effect. Furthermore, there have been multiple non-surgical treatment packages developed for trials comparing meniscectomy and non-surgical care, with good results.(22). In the feasibility study that preceded this main trial (4) we delivered a package of optimised rehabilitation which we called Personalised Knee Therapy. We will do the same in this main trial.

There is an urgent need to assess the clinical and cost-effectiveness of MAT against best non-surgical care. The UK currently spends an estimated £2M annually on MAT. This is increasing without evidence that it is clinically more effective than non-operative treatment or cost-effective. If MAT is more effective than alternative non-operative treatments, then it could reduce pain, disability and costs over many years in young people for whom there are few alternative treatments. However, if it is not more effective than non-operative treatment or if not cost effective, then expenditure on MAT should be re-considered.

1.3 Research question

For people with pain after a meniscectomy, but without established OA, does a treatment strategy of undertaking MAT surgery or Personalised Knee Therapy result in better clinical and/or cost effectiveness outcomes?

1.4 Ethical considerations

The trial will be conducted according to the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the UK GDPR.

Participants will be randomised to either surgical or non-surgical care. This is a major decision for patients and will require good quality consent materials and information, both at the time of consent and ongoing after the trial. We will not restrict participants from further treatment (such as additional surgery outside the trial protocol), this will be at their own discretion and the discretion of a clinician who treats them. We will ensure that both treatment options are valid and reasonable forms of treatment and when 2-year follow-up analysis is complete, we will inform participants of the findings of the study to help their future treatment decisions.

1.5 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194).

1.6 Assessment and management of risk

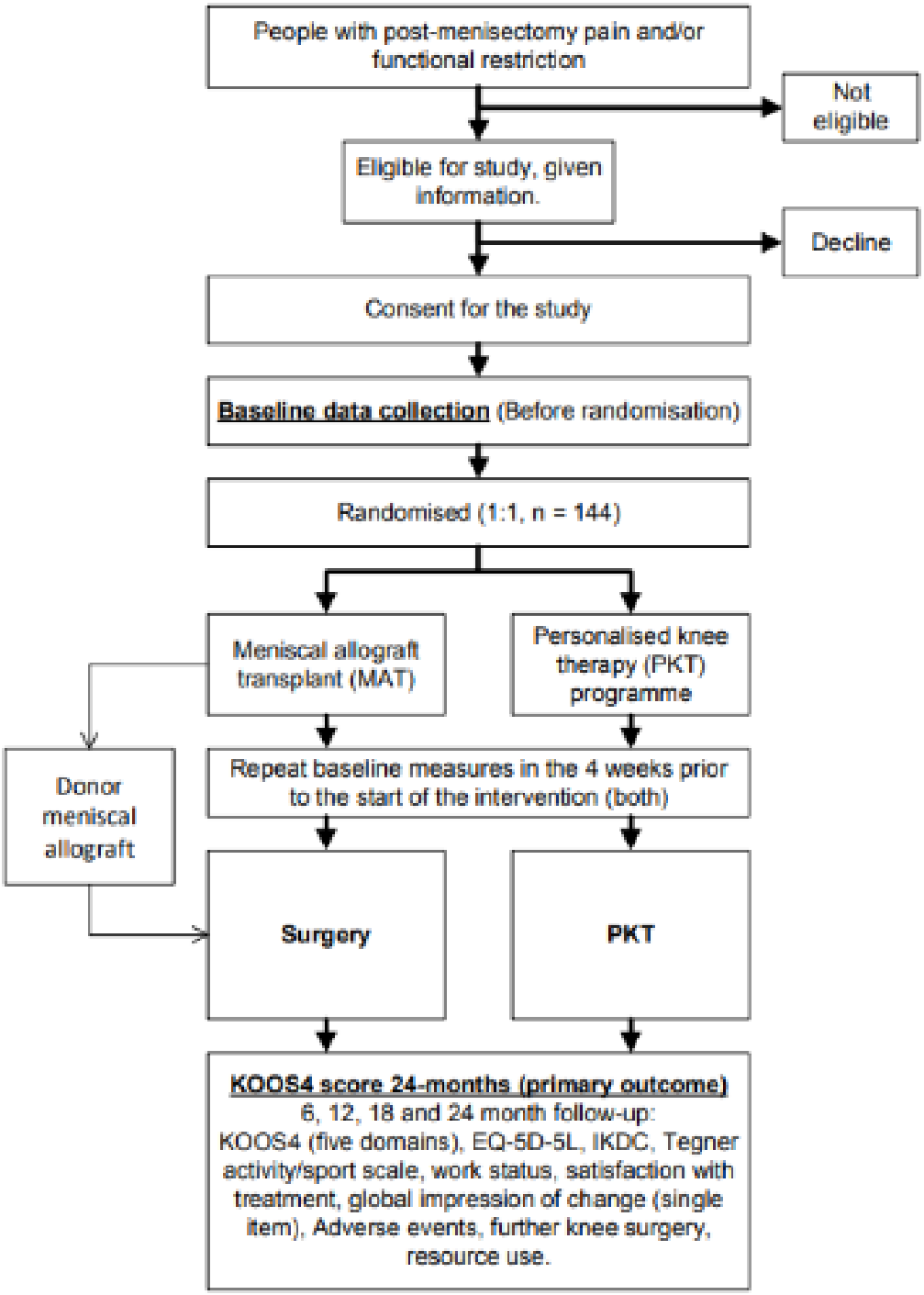
The interventions are both standard interventions, used in the NHS at present. Inevitably, there is additional risk related to the surgery group as any operation has inherent risks, but not beyond what is normal for NHS practice. A risk assessment will be performed according to Warwick Standard Operating Procedures (SOP) and a monitoring plan developed depending on the risks identified. Risks specific to the trial include risks of data breaches, incorrect allocation, or failure to recognise safety concerns. These risks will all be carefully managed by following Warwick CTU SOPs and careful adherence to the principles of Good Clinical Practice (GCP).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

MeTeOR2 is a two-arm, multi-centre pragmatic randomised controlled trial to assess the clinical and cost-effectiveness of MAT compared to optimised rehabilitation, using a package that we have termed Personalised Knee Therapy (PKT).

Figure 1 Trial flow diagram



2.2 Aims and objectives

The overarching aim is to determine whether a treatment strategy starting with MAT or PKT is the most clinically effective and cost-effective approach, for people with post-meniscectomy pain and functional loss.

2.2.1 Primary objective

1) The primary objective of this trial is to compare the clinical effectiveness of an initial treatment strategy of MAT compared to PKT, based on participant-reported knee function at 24 months post randomisation, using the four-domain version of the Knee Injury and Osteoarthritis Outcome Score (KOOS4).

2) The primary cost-effectiveness objective is to determine the cost-effectiveness of MAT compared to PKT from an NHS and Personal, Social Service (PSS) perspective.

2.2.2 Secondary objectives

3) To quantify and draw inferences on, health utility, occupational status, sports participation, mental wellbeing, further treatment (including further surgery or physiotherapy in either arm) and adverse events based on:

    - The KOOS4 at baseline, pre-intervention, six, 12- and 18-months post randomisation.
    - EQ5D-5L at baseline, pre-intervention, three, six, 12 18 and 24-months post randomisation
    - The five individual KOOS domain at baseline, six, 12-, 18- and 24-months post randomisation.
    - International Knee Documentation Committee subjective score (IKDC) at baseline and 24 months post randomisation.
    - Short Warwick-Edinburgh Mental Wellbeing Scale at baseline, six, 12-, 18- and 24-months post randomisation.
    - Tegner activity/sport scale at baseline, six, 12-, 18- and 24-months post randomisation.
    - Satisfaction with the outcome of treatment at, six, 12-, 18- and 24-months post randomisation.
    - Patient global impression of change at, six, 12-, 18- and 24-months post randomisation (a single question, with seven response options).
    - Adverse events at six, 12-, 18- and 24-months post randomisation.
    - Further knee surgery at six, 12-, 18- and 24-months post randomisation.
    - Health resource use at baseline, six, 12-, 18- and 24-months post randomisation.
    - Analgesia use at baseline, six, 12-, 18- and 24-months post randomisation

4) To evaluate process measures to compare days to initiation of treatment, rehabilitation attendance and participant expectation of outcome (in terms of Tegner score, as used in ACLSNNAP).

2.3 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

Inclusion criteria:

1. **Pain and/or functional restriction from the knee**, severe enough to warrant potential MAT in the judgement of the treating clinician.

2. **Previous meniscectomy** ≥ six months ago.

Exclusion criteria:

1. **Symptomatic ligament instability,** not previously corrected, as determined by the assessing clinician.*

2. **Coronal limb alignment which requires surgical correction,** (previous correction, performed at least 6 months before entry to the trial, is not an exclusion criteria), as determined by the assessing clinician.*

3. **Age under 16,** or if ≥16, open growth plate at the proximal tibia as judged by the clinical team on imaging taken as part of standard care.

4. **Full thickness cartilage loss (exposed bone) >1cm^2** on routine clinical MRI, prior surgery, or any other form of clinical imaging or evaluation. This will be determined by the assessing clinician (it could be based on an assessment by a clinician or a radiologist, although the final decision rests with the treating clinician).

5. **Inflammatory arthritis affecting the study knee** as determined by the assessing clinician (i.e., a prior inflammatory event not considered to be related to the current clinical condition would not require exclusion).

6. **Unable or unwilling to engage with rehabilitation**.

7. **Unable to adhere to trial processes.**

8. **Previous randomisation in the present trial** (i.e., other knee). Where a previous randomisation has occurred in error, a participant may be withdrawn and this criterion will not apply.

*Previous surgery (except prior MAT) will be allowed. Where people have mal-alignment or ligament deficiency (30% of the MAT population), alignment or ligament deficiency may be corrected by osteotomy or ligament reconstruction, which should have been performed at least six months before entering someone into the study.

2.4 Participant identification / Screening

Participants will be identified by clinical teams delivering normal clinical care, although we accept that patient pathways will differ between sites. They may typically be identified from outpatient or intermediate care clinics, hospital waiting lists or referrals into hospital (from either primary, intermediate, or secondary care). The exact location of recruitment will not be a specific requirement, to allow flexibility between different sites as patient pathways will differ, but there is a requirement that any potential participant should be evaluated by a clinician able to judge the eligibility criteria.

In this trial, we anticipate there may be many people who are not initially seen in a trial site or expert centre. There are likely to be many more people in the community with this clinical problem for whom this treatment is not usually offered. To recruit successfully, we will need to have a referral pathway in place for potential participants to be referred, for consideration if participation in the trial.

The study will be widely advertised to clinicians (primary and secondary care) involved in musculoskeletal care as well as knee surgeons (through the British Association of Knee Surgeons, BASK, or other similar organisations) and the wider orthopaedic community. We may promote the study through social media or news outlets. Where a potential participant is identified by someone in clinical care who is unable to assess eligibility or is not in a trial site, they will be referred through normal clinical channels to a centre or person that is able to do so, this is expected to be a common mode of identifying participants. We will also open Participant Identification Centres in units who are willing to do so.

Even outside of any study advertising (such as reports in the news, or social media), our study websites, study related publicity, and social media accounts will be open access and it is not uncommon for members of the general public to contact either their own clinicians or the trial team to offer to participate. Where this happens, they will be directed to participating sites where appropriately trained clinicians will assess eligibility and provide appropriate study information, via the routine referral process in the health service.

Participants who are identified in trial sites as potentially eligible will be provided with verbal and written information. Eligibility will be confirmed by an assessing clinician listed on the delegation log who is capable of confirm eligibility based on their current role, skills, and knowledge.

There is no requirement for any specific investigation, the eligibility criteria can be assessed by routine clinical evaluation. It is normal clinical practice to evaluate someone with a painful knee after prior surgery with MRI scan for diagnostic purposes before any consideration of treatment options, this is likely to be the case for most of our participants but is not a requirement for entry (for example, someone with a pacemaker may be investigated differently) and prior investigations will follow normal clinical practice. Some clinicians may use x-rays to clinically evaluate a patient as part of their routine practice, but there is no requirement for the use of ionising radiation to enter the trial.

The assessing clinician will confirm appropriateness for study eligibility on a case report form (CRF) based on clinical assessment and standard care imaging for that site. Potential participants suitable for inclusion will be given information about the study and invited to discuss the study further with a member of the research team, they will be given adequate time to consider study participation (see below). Depending on the study process at individual sites, information sheets may be posted or emailed to potential participants. A

member of the local research team will carry out the informed consent process (see 2.6), registration and baseline data collection.

A screening log will be completed at all sites and emailed to the co-ordinating centre monthly or completed directly on to the study database (with any identifiers redacted, except numbers for trial participants). This will include details of the number of people presenting to recruiting clinical teams who are considered suitable for meniscus allograft surgery, and the number who consent to enter the study. This data will be used to populate the CONSORT statement in the study report.

2.5 Site Staff Training

The Trial Manager(s) will provide training prior to recruitment to the local Principal Investigator (PI) and all clinical and research team members who will be responsible for conducting trial related procedures including confirming eligibility, obtaining consent, performing interventions, collecting baseline data and subsequent SAE reporting. The PI will also cascade training to members of the team as required.

The trial coordination team will perform site initiation visits and will provide training tips via a presentation outlining the overview of the trial (key personnel, protocol, management, and oversight) CRF completion, trial specific training (surgical plan, rehabilitation package and outcome assessment training), SAE reporting, withdrawals, screening log and data clarifications. A training log will be used to document who has received training and this log will be held in the ISF, research staff taking part in the study will sign the site delegation log (along with a confirmatory signature from the PI) and update the trial coordination team when a new member joins the research team or the local PI changes.

2.6 Informed consent

The local Principal Investigator retains overall responsibility for informed consent at their site and must ensure that any person listed on the site delegation log with the delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent.

The investigator or their nominee, for example a member of the research team (research associate or research nurse), will provide both written and verbal information to inform people what participation in the study entails. They will also answer any questions that the person may have concerning study participation. Options for taking consent are listed below.

Recruitment will be open to people from 16 years of age (who meet the inclusion criteria). This problem can affect older adolescents (not those with remaining tibial growth potential, where clinical decision making may differ) in the same way as people over 18 and such individuals will be encouraged to share this with their parents as appropriate. Our consent process and information sheets/media will be carefully designed with the aid of our PPI team members to ensure that all of those invited to participate in the study are well informed prior to providing consent.

It will be explained that entry into the study is entirely voluntary and the right of any person to refuse participation without giving reasons will be respected and recorded on the screening log. They may be provided with a contact point where they may obtain further

information about the trial if requested. The participant will remain free to withdraw from the study at any time without giving reasons and without prejudice to any further treatment (see 2.8.2). The participant will also be free to discontinue study treatment or study follow-up, at any time without giving a reason (whether or not they continue in the study for the purposes of collecting data). Participants will be informed during the informed consent process that any data collected, apart from that which is identifiable, will be kept.

If a person loses capacity to consent, with no expectation that they will regain it, then they will be treated in a consistent way as someone who has withdrawn (that is we will retain data up to they lose capacity). If they regain capacity, we will assume that their previous consent stands, unless they specifically withdraw, and will resume data collection activities.

Any new information that arises during the trial that may affect the participant's willingness to continue in the trial will be discussed with the participant and, if applicable, renewed consent will be obtained using an amended consent form.

Participants' GPs will usually be informed by letter that they are taking part in this clinical trial. Participants may decline their GP being informed of their participation in the trial involvement by not initialling the appropriate box on the consent form.

The principal investigator or their nominee and, if applicable, the independent witness (see below) must sign and date the consent form (see 2.6.2). One copy of this will be posted to the participant, one will be kept by the investigator/nominee and filed in the ISF, and a third will be retained in the patient's hospital record.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the study, the participant information sheets, and consent form.

2.6.1 In-person consent

Potential participants who are identified as above at the study sites, will be given study information and adequate time to consider participation and will be invited to give their consent to become participants in the trial. We have not set a minimum time period as some people will wish to consent at the time they receive the information and find additional visits a burden. Even after consent, they will have ample time to consider participation and potentially withdraw whilst waiting for their intervention, which would likely to be a number of weeks for PKT and could be many months for surgery. No participant will provide initial consent for the study on the day of surgery, but consent to remain on the trial will be re-affirmed at that point.

Potential participants who wish to take more time to consider participation will be given the opportunity to do so and, will be offered the option of a further visit or they will be provided with information and a consent form to take away. Sites will follow-up with a telephone call to discuss the study, answer any questions and ascertain if the patient agrees to participate. If the potential participant agrees, they will be able to complete the consent form at the time, return the signed consent form by post in a pre-paid envelope, a follow-up visit can be arranged, or witnessed verbal consent will be undertaken (see below). If consent is returned by post or in person at a future date, a file note will be made to document this, and therefore explain why the countersigned and signed dates differ on the form.

2.6.2 Witnessed verbal consent

A witnessed remote verbal consent process is an option in this study, as it allows for people who may otherwise have a long distance to travel. Witnessed remote verbal consent will be gained via telephone or any Trust approved online video consultation platforms. The call/video call must be witnessed by a site staff member who will declare that consent was appropriately given, study explained, questions answered, and time given for participants to make a decision. After remote verbal consent is given, a paper copy of the current consent form will be signed by the clinician delegated to consent and countersigned by the independent witness. A copy of the signed consent form will be given to the patient (via post or in person when possible). Participants are not required to sign the paper consent form if they have consented via the witnessed remote verbal consent process. However, the detailed process will be described in the participant's notes and a copy of the countersigned consent filed together.

The process for witnessed verbal consent should also adhere to local site policies for this in all cases.

Trial procedures (i.e., those that occur after consent) including baseline assessments and randomisation will not be undertaken until witnessed remote verbal consent or written/signed informed consent has been given and appropriately recorded in the patient's medical notes.

2.8 Randomisation

2.8.1 Randomisation

Participants will be randomly allocated (1:1) to the two treatment groups via a central computer-based randomisation system provided by the Warwick Clinical Trials Unit's programming team (WCTU, independent of the study team) after consent has been obtained and baseline data have been collected. Randomisation will be 1:1 allocation by minimisation with a random factor with a 70% weighting towards balance across the whole study, stratified by age (greater or equal to 30, or less than 30), centre and knee compartment (lateral or medial).

Randomisation will be performed by any member of the local clinical or research team on the delegation log, using the online system. A back-up automated telephone system will be available 24 hours.

In the event that neither of these options are functioning or available, sites can contact the study team on working days.

Participants will be randomised sequentially at site level.

Stickers, electronic tags or equivalent may be used on the participant's clinical notes to flag their inclusion in the trial, depending on local site arrangements for flagging inclusion in trials.

2.8.2 Post-randomisation withdrawals

Participants may choose to discontinue trial treatment and/or withdraw from the trial at any time without prejudice. Unless a randomised participant explicitly withdraws their consent for follow-up (even if they discontinue consent for the allocated intervention), they

will be followed-up wherever possible and data collected as per this protocol until the end of the trial. Routine NHS datasets related to their care, for which they have consented (such as Hospital Episode Statistics, National Joint Registry and Scottish Arthroplasty Project) may be examined for adverse events (such as re-operations) unless they also specifically withdraw from this aspect on the withdrawal CRF or consent forms. Participants who are registered, but not yet randomised may withdraw at any time, they will not be considered to have entered the study. Should a participant withdraw from the trial, before or after randomisation, they will continue to be treated according to normal clinical practice. A withdrawal CRF should be completed to record their decision. Data collected up to the point of withdrawal will be retained.

Participants may be withdrawn from the trial at the discretion of the Chief Investigator and/or Trial Steering Committee (TSC) or Data Monitoring Committee (DMC) due to safety concerns. Needing to change the intervention for safety reasons after randomisation is not a reason for withdrawal, participants would be kept in the study and their data included on an intention to treat principle. Some participants may not undergo the allocated intervention either as a personal decision or a clinical decision after randomisation (for example, a change in health status, or an improvement in symptoms), in which case they will be managed according to the best judgement of the treating clinician but will be kept in the study for the purposes of data collection on an intention-to-treat basis. If an intervention is delayed, the allocated intervention could then be delivered later at an appropriate time, or not at all, based on the decision of the clinical team. Participants will be allowed to have other treatments including other surgery as determined by the clinical team, although adherence to the allocated intervention will be encouraged where possible.

2.9 Trial treatments / intervention

2.9.1 Trial treatments

A full summary of the surgical and PKT interventions will be available in MeTeOR2 manuals, prepared following surgical and non-surgery consensus meetings to which applicable co-investigators and relevant staff from participating sites will be invited.

These will be made available on the MeTeOR2 trial webpage for ease of access for participants and sites.

2.9.1.1 Surgical treatment:

MAT surgery will be done once an allograft becomes available and will follow a trial-specific surgical manual. The content will be developed at a surgical consensus meeting and will be informed by the International Meniscus Reconstruction Experts Forum (IMReF) guidelines (led by co-applicant A. Getgood).

No immunosuppression is required as meniscal allografts have low cellular content and are not rejected in the way solid organ transplants might be. Donors are screened for blood-borne diseases according to approved tissue bank policies. Essentially this is similar to blood donors and there are no reported cases of viral transmission from MAT.

Many people wait six to 12 months for a graft of the right size to become available (median 6.5 months in our pilot study). To reduce time to surgery, the dimensions of the graft needed will be sent to multiple tissue banks according to surgeon preference and usual practise. The first bank to have the size available will be used. Of note, with the change to

presumed consent for organ donation, we expect UK supply to increase. Once a graft becomes available, surgery is typically prioritised. This is normal practice in the NHS for MAT (as with many other transplants).

The delay to receive a graft is unavoidable in meniscal transplantation surgery, due to the availability of a suitable sized donor graft from tissue banks. Following the pragmatic design of the trial, this is part of what is being studied and is inherent to the intervention. Recovery plateaus after nine to twelve months from surgery. As the primary outcome is at two years, recovery will still be completed by the primary outcome time point, even for people in whom surgery is delayed.

All care, including the choice of anaesthetic, the surgical procedure, and post-operative analgesia, will be in accordance with usual procedures and care at participating sites. Fidelity and process measures will be assessed using a surgical case report form which will include details of surgery (surgical findings, theatre time, tourniquet time, graft size, fixation of graft, any other procedures) and the anaesthetic on a case report form (CRF).

Rehabilitation for the surgery group will be according to a standardised programme specific to MAT. We will use the lead centre's established programme for this and, in discussion with participating centres, adapt it to ensure it is deliverable across multiple NHS and international sites in a multi-centre trial. This will be led by the physiotherapy co-applicants in parallel to the refinement of the PKT intervention. A formal PKT programme will not be used prior to surgery in the MAT arm, although we will not discount people having prior or current physiotherapy.

2.9.1.2 Personalised knee therapy (PKT)

The PKT programme is an optimised non-surgical intervention (i.e. optimised rehabilitation) to improve the outcomes of people with knee pain and/or functional limitation following meniscectomy.

We will use PKT programme developed for the pilot, an evaluation of current relevant literature and a consensus meeting to develop the final PKT programme for the trial. The non-surgical consensus meeting will update the pilot programme and ensure that this is deliverable across our study sites. This will also be conducted in close interaction with patients, physiotherapists at NHS trusts and other stakeholders, taking relevant guidelines into consideration.(6,18-21)

In addition, we will inform the development of the PKT package with the results from a systematic review of outcomes after operative and non-operative treatment of meniscal tears (PROSPERO:122179).(16), a systematic review of predictors of outcomes from non-surgical management of meniscal tear(23), and the non-surgical interventions for early OA as part of our HTA Evidence Synthesis for 'Surgery for Early Osteoarthritis' (CI: A.Price, NIHR HTA). These findings will provide an evidence-based foundation against the original PKT programme. These comprehensively demonstrate the evidence-base on non-surgical interventions such as physiotherapy in addition to other non-surgical interventions such as weight loss advice or referral to services and braces or orthotics for knee pain (43).

We will convene a non-surgical care consensus group in the set-up period to review the PKT programme. We will consider if areas of the programme should be delivered through digital means (website and/or app) and confirm with physiotherapists from participating units that

the programme will be deliverable at sites. It is expected that both written and digital information will be available.

The envisaged PKT programme is outlined below:

PKT Aim: To reduce pain, restore full knee range of motion, improve knee function and optimise overall social participation through a goal-setting approach personalised to the participant.

Delivered by: A senior physiotherapist trained in the principles of PKT

Mode of delivery: The intervention will be personalised to the participant. Through this there is flexibility, as determined by clinical judgement and service provision at the time, for PKT to be delivered face-to-face, through virtual consultation or a hybrid of the two.

Duration: Minimum of three months from first assessment and a minimum of four sessions in total, but would be as many as clinically required, reflecting normal clinical practice.

Treatment starting point from randomisation: when an appointment with a physiotherapist is available according to normal clinical waiting times. Typical waiting times for physiotherapy appointments at the lead site are approximately 2-3 months, but this may vary depending on individual sites' usual processes.

Timing of consultations: The interval between consultations will be personalised to the needs of the participant based on the progress, presentation, and treatment goals. This will be a shared decision between physiotherapist and participant.

Content of consultations: Assessment: All participants will be reviewed in an initial assessment by a physiotherapist. In this, participant's history (subjective assessment) and physical examination (objective assessment) will be taken. This will follow a routine musculoskeletal physiotherapy assessment. Specific focus in the objective assessment will be made on lower limb function and kinetic control, muscle length, strength, and recruitment. Shared goals will be discussed between physiotherapist and participant which will form the basis of the problem list and treatment plan.

Content of consultation: Treatment: Based on the goals developed by the physiotherapist and participant, and problem list identified from the assessment, an agreed treatment plan between physiotherapist and participant will be made. Through this, the physiotherapist will deliver interventions aimed to specifically manage the presenting problem. Through this, a personalised approach is made to the participants rehabilitation, optimising their outcome. This is summarised in the table below. Through this, the physiotherapist and participant, through discussion and clinical reasoning, select intervention from the table below, in a menu-approach, to personalise the rehabilitation to the participant. The specific exercises, interventions, dosage, intensity and frequency of exercise will be determined by the presenting participant and prescribed accordingly by their physiotherapist. This ensures a personalised programme is offered as part of PKT (and is consistent with good quality physiotherapy care in routine practice).

PKT Treatment Table

Presenting problem	**Potential Treatment**

Increased knee pain	Advice on analgesia; behaviour modification; thermal treatment; foot assessment for orthotics or braces; weight loss advice and/or referral to weight loss programmes or services
Reduced lower limb muscle length	Stretching exercise programme (notably hamstring, calf complex, quadriceps, hip flexors)
Reduced lower limb strength	Open or closed kinetic change, functional, progressive strengthening programme (notably glutei, quadriceps, hamstring muscle groups); gym programme
Work limitation	Occupational advice; structured exercise programme; behaviour modification; pacing
Sport/activity limitations	Sporting/exercise analysis, sport/activity-specific exercises; graded exercise progression; sports performance modification
Increased knee instability	Functional recruitment/strengthening exercises; proprioceptive programme; taping or bracing where appropriate
Increased knee swelling	Compression dressing/bandage; thermal treatments; medication advice; behaviour modification; elevation
Reduced core stability	Progressive core stability programme e.g. supine to sitting to standing to function aiding recruitment and control of abdominals and glutei

Table 2: PKT Treatment Table

In relation to the exercise elements of the plan, both in the consultation and home settings, participants will be required to work through three phases, based on the Borg Rating of Perceived Exertion (see below). Using this, participants will be asked to initially exercise aiming for a Borg rating of 1 to 3 (Initial Phase). If participants can complete the prescribed exercises, as determined by the physiotherapist using the PKT Treatment Table above, with a numerical rating pain score of 0 to 3 for two weeks and have moderate to minimal knee swelling, they will be asked to progress exercising to a Borg Rating of 4-5 (Mid-Phase). If this can be sustained for a further two weeks with a numerical rating pain score of 0 to 3 and minimal knee swelling, they will be asked to progress to a Borg Rating 6 to 7 (Final Phase). Through this, the intensity of exercise is moderated by the participant's perception of their pain and exertion to ensure that sufficient load is achieved, by personalised to their capabilities. If the participant experiences a symptom flare, then they can moderate to a previous Phase and the build-up accordingly.

Figure 2: Borg Rating of perceived exertion

Borg Rating of Perceived Exertion	
0	Nothing At All
0.5	Very, Very Light (Just noticeable)
1	Very Light
2	Light (Weak)
3	Moderate
4	Somewhat Hard
5	Heavy (Strong)
6	
7	Very Heavy
8	
9	
10	Very, Very Heavy (Maximal)

Supportive materials for home exercises: The in-consultation programme will be supported through a home exercise plan, mirroring the interventions delivered in the consultation. This will be supported with materials delivered as a workbook, online or through an App, dependent on the participant's preference. These will include a summary of the goals developed and treatment plans personalised to the goals, explanation on the home exercise programme and logs to aid home exercise adherence of participant use only, in addition to goal-setting sheets to aid further problem-solving and goal-setting skills.

The appreciation of both the individual health challenges which this group of patients experience to ensure a 'personalised' rehabilitation programme, aligned with a comprehensive programme of non-surgical interventions such as weight loss advice and referral or provision of braces and orthoses, ensure this is an optimised therapy.

2.9.2 Compliance/contamination/adherence

This has been addressed in 'process and fidelity measures' in outcomes. Attendance to no physiotherapy visits will be considered non-compliance with either PKT or post-operative rehabilitation. Attendance to less than four sessions of PKT or post-operative rehabilitation will be considered partial compliance.

2.10 Co-enrolment into other trials

Co-enrolment will not normally be recommended especially of trials that might influence pain or function of the lower limbs, but individual requests can be discussed with the TMG to determine if these will affect the delivery or conduct of the trial.

2.11 End of trial

The trial will end when all participants have completed their 24-month follow-up, although this will be extended if we receive funding for five, ten or even 15–20-year follow-up (we will obtain consent for long-term follow-up at baseline).

Elements of the trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC) or Trial Steering Committee (TSC). (Note: If the DMC recommends stopping, this recommendation will be reviewed by the TSC prior to stopping the trial).
- There is urgent safety information that warrants stopping the study immediately, in which case the study will be temporarily stopped pending discussion with the DMC and/or TSC.
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if all trial related activities are terminated early.

3. METHODS AND ASSESSMENTS

3.1 Outcome measures

3.1.1 Clinical measures

In the absence of a published core outcome set, outcome measures were selected following PPI consultation and interaction with our experienced clinical team. This ensured that we have chosen appropriate measures in a timeframe which captures the important factors of recovery and symptoms without placing a burden on the participants. Patients particularly emphasised the importance of psychological, work and sporting outcomes as well as more traditional pain and function measures. We have piloted our outcome set with patients who agreed they were appropriate to their problem and were not an excessive burden.

We have been funded to collect outcomes up to 24 months but will seek future funding for five and ten year follow-up as well as collection of data from routine datasets (such as NHS digital or other country-specific equivalents). We will consent for these activities at baseline.

Primary outcome:

- The four domain **Knee Osteoarthritis Outcome Score (KOOS4)** score 24-months after randomisation. This is a 25-domain knee-specific instrument (0-100, 100 best score) the sum of four of the five domains of the full KOOS score (KOOS4 uses the domains for symptoms, pain, function/sports and quality of life, but not activities of daily living).(24) KOOS4 has been widely used in previous trials in knee surgery including young adult non-arthritic populations such as this one and is well accepted by the clinical community.(6,7,25-27)

Secondary Outcomes:

- The **KOOS4** (four domains) at pre-intervention, six, 12- and 18-months post randomisation. See above.

- The five individual **KOOS** domains at baseline, six, 12-, 18- and 24-months post randomisation and composite KOOS5 score: A validated knee specific instrument developed to assess the patients' opinion about their knee and associated problems.

- **IKDC** at baseline and 24 months post randomisation: Has been subjected to rigorous statistical evaluation and has proven to be a valid and responsive patient-reported outcome measure.

- **EQ-5D 5L** at pre-intervention, three, six, 12-, 18- and 24-months post randomisation: Is a validated, generic health-related quality of life measure consisting of five dimensions each with a five-level answer possibility. Each combination of answers

can be converted into a health utility score. It has good test-retest reliability, is simple for participants to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.(57, 58)

- **Short Warwick-Edinburgh Mental Wellbeing Scale** (SWEMWBS) at six, 12-, 18- and 24-months post randomisation.

- **Tegner activity/sport scale** at six, 12-, 18- and 24-months post randomisation.

- **Satisfaction with the outcome of treatment** at six, 12-, 18- and 24-months post randomisation using a 5-point Likert scale.

- **Patient global impression of change at** six, 12-, 18- and 24-months post randomisation. A simple 7- point scale assessing perception of improvement.(59)

- **Adverse events** at three, six, 12-, 18- and 24-months post randomisation, see section 2.3.2.

- **Further knee surgery and further knee physiotherapy** at six, 12-, 18- and 24-months post randomisation. This will be collected for both groups.

- **Pain** at six, 12-, 18- and 24-months post randomisation.

- **Resource use** at six, 12-, 18- and 24-months post randomisation. The primary analysis will concentrate on direct intervention and healthcare/personal social services costs, while wider impact (societal) costs will be included within the sensitivity analyses. Relevant resource use questionnaires will be administered to participants at baseline and all follow-up points, to collect resource use data associated with the interventions under examination.

At baseline, we will collect KOOS4 and all five KOOS domains, IKDC, EQ5D, SWEMWBS and the Tegner scale. We will also collect details about previous treatment, duration of treatment, analgesia use, work or educational status, knee range of motion, age and body mass index.

As an additional pre-intervention baseline (to understand any changes occurring whilst people wait for intervention, given the potential discrepancy in the between groups), we will collect EQ5D and KOOS4 scores in the 4 weeks leading up to the intervention.

We will collect data at baseline on equality and diversity measures (as recommended by the NIHR HTA programme) to include: geographical location (postcode district of home address); age; other disabilities; gender reassignment; marriage and civil partnership; pregnancy and maternity; ethnicity; religion or belief; sex; sexual orientation;

socioeconomic status (employment status and index of multiple deprivation based on postcode). These will not be used for statistical analysis but will be monitored by the Trial Management Group as the study progresses and will be reported in aggregate at the end of the study as a measure of the representativeness of the study population to the population of interest.

Process and Fidelity Measures

- **Days to initiation of randomised treatment**, defined as the number of days between randomisation and the first therapy contact for those who undergo PKT or the day of surgery, whichever is received first regardless of allocation.

- **Physiotherapy attendance** will be collected on participant CRFs (regardless of allocation) and from records of participating hospitals, where we are able to collect this.

- **A surgery form** with details of the surgery delivered (such as mode of fixation of menscal roots, type of suture fixation and any additional surgery performed)

- Participant expectation of outcome will be recorded at baseline.

- Alongside routinely collected data in screening logs, we will also collect the source of referral (as primary care/secondary care/participating site, and by geography) to assess referral patterns during the trial.

3.1.2 Safety

Adverse Events and Serious Adverse Events will be managed following GCP guidelines and Warwick SOPs. Details of this are given in section 4 of the protocol.

3.1.3 Health economics measures

A prospectively planned economic evaluation will be conducted from a NHS and personal social services perspective, according to the recommendations of the NICE reference case.(28) Given multinational recruitment, we will consider inter-country healthcare differences in constructing our data collection tools and analysis plan.(28,29) Health service and social service contacts, made in connection with their treatments, will be recorded as part of the resource utilisation questionnaires. Time lost from work (paid/unpaid), will also be recorded.

3.2 Schedule of delivery of intervention and data collection

Table 3: Schedule of delivery of interventions and data collection.

Visit/follow up number	-1	1		2		3	4	5	6	7
Visit/follow up	**Screening**	**Baseline**	**Pre Intervention Baseline** *(if over 6 months since visit 1)*	**Intervention**	**Medical note review**	**3 Months follow up**	**6 Months follow up**	**12 Months follow up**	**18 Month follow up**	**24 months follow up**
Time after v1 (±window)	-	0		*data <4w of int start*		3 months (-2 to +6w)	6 months (±6w)	12 months (±3w)	18 months (±6m)	24 months (±6m)
Check eligibility	✓									
Invitation to study	✓									
Informed consent		✓								
Medical history		✓								
Inclusion/exclusion criteria		✓								
Randomisation		✓								
Intervention (Surgery/PKT)				✓						
Operation note				✓	✓					
KOOS4		✓	✓	✓			✓	✓	✓	✓*
IKDC Questionnaire		✓	✓	✓						✓
EQ-5D 5L		✓	✓	✓		✓	✓	✓	✓	✓
Health resource use			✓			✓	✓	✓	✓	✓
SWEMWS		✓	✓	✓			✓	✓	✓	✓
Tegner activity scale		✓	✓	✓			✓	✓	✓	✓
Satisfaction with outcome of treatment							✓	✓	✓	✓
Patient global impression of change							✓	✓	✓	✓
Complications, AEs and further surgery					✓	✓	✓	✓	✓	✓
Days to initiation of treatment					✓	✓	✓	✓	✓	
Rehabilitation attendance					✓	✓	✓	✓	✓	✓

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events

An Adverse Event (AE) will be defined in this study as any untoward medical occurrence in a participant taking part in health care research, which does not necessarily have a causal relationship with the research. However, for the purposes of this study, and to avoid unnecessary recording of events, we will only collect AEs related to their knee and to the treatment they receive in the study (or any treatment for their knee) or related to trial processes.

4.1.2 Recording adverse events

AEs related to the MAT procedure including the surgery, anaesthetic, post-operative care and rehabilitation, any component of the PKT package, or any knee treatment in the AE reporting period will be recorded on the appropriate case report form (CRF) for return to the trial central office and reported to the relevant oversight committees.

AEs will be collected from the point of randomisation onwards, up to 24 months.

Some events which occur during treatment and recovery will be considered normal aspects of the therapy, anaesthetic and post-operative recovery process and will not need reporting unless in the opinion of the clinical team, they are untoward, excessive, or outside of what might normally be expected for the procedure. The are normal events that occur frequently after physiotherapy or surgery and 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 or post-intervention pain in the first 6 months (note that pain after 6 months will be collected as an outcome in the study, using the KOOS pain domain).
- Numbness on the lateral side of the surgical wound.
- Early wound oozing which spontaneously resolves.
- Swelling, within the confines of what is considered normal post-intervention swelling by the treating clinical team.
- Restriction of range of motion, within the confines of what is considered normal post-operatively by the treating clinical team.
- Bruising, unless this is considered abnormal by the treating clinical team.
- Post-intervention pain, muscle soreness or tiredness during or after physiotherapy (in-patient and out-patient) in either group.

All recorded adverse events will be monitored for trends, see section 4.2 for responsibilities. An outcome of ‘not yet resolved’ is an acceptable final outcome for non-serious AEs at the end of a patient’s participation in a trial

4.1.3 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is an important medical condition.

Further knee surgery will be considered an outcome regardless of allocation (see 3.1.1). Persistent pain without new pathology or other event will not be considered an SAE as this will be recorded in outcome scores.

4.1.4 Reporting SAEs and Related SAEs

The SAE form should be completed and emailed to the study resource account and the wctuqu@warwick.ac.uk resource account in the first instance.

All **SAEs,** (except for the normal events listed in 4.1.1 which will be recorded as outcomes occurring from the time of randomisation until 24 months post-randomisation, must be detailed on the SAE Form and reported via email to the central study team, (WCTU@warwick.ac.uk), **within 24 hours** of the research staff becoming aware of the event.

Should the PI be unable to report within 24 hours, or is unavailable, any nominated person on the delegation log may send an unsigned SAE form. Further details should then be sent by site as soon as practically possible.

Events occurring before randomisation will not be recorded.

Any change of condition or other follow-up information should be emailed to the central study team 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 SAEs at database lock.

AEs or SAEs may be identified by the coordinating centre from the CRFs, either from specific questions or from answers within PROMs. If this occurs, the coordinating centre may query the site for details of the event for the purposes of the sites own clinical governance. This will be determined on a case-by-case basis, and the potential to do so will be included in the participant information sheet (PIS).

The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. Events which are conclusively assessed by the Principal Investigators and Chief Investigators as possibly, probably, or definitely related to the trial intervention and are unexpected will be reported to the REC within 15 days.

4.1.5 SAEs Exempt from Reporting

As with AEs in 4.1.4, SAEs will only be reported where there is an untoward medical occurrence in a participant related to their knee and to the treatment they receive in the study (or any treatment for their knee), or related to trial processes. Other events that do not meet this definition will not be reported. Normal events defined in 4.1.2 will not be reported as adverse events or serious adverse events.

4.1.6 Assessment of Causality

A clinically qualified member of staff that has been appropriately delegated by the PI should perform an assessment as to whether there is a possibility that the event has occurred as a result of the study intervention. An independent assessment will also be performed by a delegate of the Sponsor. If either the PI's delegate or the Sponsors delegate determines that there is a possible causal relationship with the intervention or its associated procedures an expectedness assessment will be performed by a delegate of the Sponsor at WCTU.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form using the following descriptions:

Relationship to trial medication	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 or device). There is another reasonable explanation for the event (e.g. the patient'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 or device). However, the influence of other factors may have contributed to the event (e.g. the patient'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.

Table 4: SAE causality

4.1.7 Assessment of Expectedness

Where SAEs are reported, an evaluation of expectedness will be made by the Chief Investigator or their delegate, using the list below. All SAEs, regardless of whether or not they are expected, should be reported according to the processes laid out in this protocol. In certain cases, the diagnoses will be confirmed, where there is uncertainty, by the treating clinician. The following are SAEs that are expected as a result of the intervention and its associated procedures:

Those related in general to surgery and anaesthetic:

- Injury to teeth, mouth, or throat during anaesthetic.
- Chest infection.
- Stroke or Cardiac Event.
- Death.
- Nerve or vessel injury due to local anaesthetic (i.e. local blocks or spinal anaesthetic).
- Spinal haematoma.

Those related to the operation itself:

- Exacerbation/persistence of knee pain beyond what is considered normal by the treating clinical team. As this outcome will be captured in Patient Reported Outcome Measures (PROMs) throughout the study, only medical interventions for persistent knee pain need to be reported.
- Restriction of range of motion, including need for manipulation under anaesthetic, arthroscopic or open procedures to relieve stiffness.
- Infection.
- Wound healing problems.
- Fracture, ligament or tendon damage or rupture.
- Meniscal graft failure, tearing or root detachment.
- For implant surgery (if performed during the study): implant failure, dislocation, or loosening
- Revision surgery or other corrective surgery.
- Thrombosis (deep vein thrombosis, pulmonary embolus, cerebral infarct).
- Damage to nerves or vessels.

Those related to physiotherapy (post-surgical rehabilitation or PKT):

- Persistent muscle soreness or muscle injury.

- Bruising.
- Swelling.
- Skin damage (for example, from bracing).

If the SAE is not listed above, the event would therefore be classified as unexpected.

4.2 Responsibilities

Principal Investigator (PI):

- Checking for AEs when participants attend for treatment / follow-up.
- Using medical judgement in assigning seriousness and causality.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within two working days of initial reporting.
- Ensuring that AEs are recorded and sent to the central study team in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Using medical judgement in assigning expectedness.
- Immediate review of all related and unexpected SAEs
- Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Production and submission of annual reports to the relevant REC.
- Monthly review of accumulated AEs/SAEs at TMG meetings.

Sponsor (University of Warwick):

- All AEs (which meet the criteria in 4.1.1) will be recorded and sent to the trial team
- Central data collection and verification of AEs, and SAEs, according to the trial protocol.
- Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of related and unexpected SAEs to the REC within required timelines.
- Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC):

- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data (without reference to allocation) and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

- In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall and by allocation group (which would typically be coded unless the committee requests otherwise) safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.3 Notification of deaths

All deaths will be reported by the CI to the sponsor. This report will be as soon as the CI becomes aware of the event. Reporting processes to other organisations (REC) will be as documented above.

4.4 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act and General Data Protection Regulation. Outside the UK, data will be handled according to local laws and regulations, although UK rules will be adhered to as a minimum standard throughout where relevant laws do not conflict.

Personal identifying information will be held at WCTU for follow-up purposes. We will also request permission from participants to retain contact details to send a summary of the study at the end of the trial. Handling of personal data will be clearly documented in the patient information sheet and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick Standard Operating Procedures (SOP 15 part 1) and the UK or local regulatory framework. There is no reason to expect this situation to occur in this trial more than any other. Data requests from participants would be handled following Warwick CTU standard operating procedures (SOP 35).

5.1 Data collection and management

5.1.1 Case Report Form (CRF) design and management

The Case Report Forms (CRFs) will be developed to collect all required trial data.

The CRFs will be developed by the Trial Manager in consultation with Chief Investigator, Trial Statistician, Health Economist, and other relevant members of the trial team. They will be produced in English initially, although translation requirements will be reviewed with the Belgian centre or if screening data reveals that language barriers are affecting participation and predominant language, or languages, can be identified.

A suitably trained member of the research team will complete CRFs directly onto the MeTEOR2 database.

Source documents are where data are first recorded, and from which participant's CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory, radiographs, and other clinical notes or correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (i.e. if there are no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant number/code, not by name.

We will minimise missing data by using multiple methods of follow-up; paper and app-based solutions (when developed) as well as telephone and text reminders, multiple contact details and clinical follow-up at 12 and 24 months.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (e.g. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.3 Data storage

All essential documentation and trial records will be stored at Warwick Clinical Trials Unit in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel. All data will be stored in a designated storage facility within Hospital sites taking part in the study, and/or WCTU. Electronic data will be stored on password protected university computers in a restricted access building.

5.4 Data access and quality assurance

All data collected will be anonymised after the collection of the baseline demographic data for each participant, except where anonymisation is not possible such as contact details for follow-up, in which case it will be kept separate from the outcome data.

Confidentiality will be strictly maintained, and names or addresses will not be disclosed to anyone other than the staff involved in running the trial. Participants will be identified by ID number, initials, and age only where necessary. Any identifiable participant data will be held separately in a locked filing cabinet and coded with the trial number to tag identifiable data to the outcome data.

Direct access to source data/documents will be available for trial-related monitoring or audit by WCTU, or ethics committees.

The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

5.5 Data Shared with Third Parties

De-identified data that underlie the results reported in the study will be available for non-commercial use, up to one year after publication of the primary outcome trial findings, or from metadata stored in a university repository up to ten years without investigator support. To access trial data, third parties must complete a data-sharing agreement with the sponsors, have an ethically approved protocol in place for use of the data, and agree the approved protocol with the MeTeOR2 TMG. 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. Analyses may include individual patient data meta-analyses or other purposes as agreed with the MeTeOR2 TMG.

Available data will include (but is not exclusive to) de-identified individual participant data that underlies the results reported in trial publications, the study protocol, statistical analysis plan, master copy of the informed consent sheets and analytic codes used.

After a year following the publication of the final report, the data will be stored in an appropriate repository, it may still be available according to the conditions laid out above but may not receive investigator support.

5.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The target difference for KOOS4, widely used across multiple RCTs, is 10 points (on a 0-100 scale); this is consistent with anchor-based studies and is accepted as a clinically meaningful difference.(7,25,26,30) This effect is similar to that found for cartilage repair in the knee in our HTA monograph on autologous chondrocyte implantation done for NICE.(3,25) We found cartilage repair to be clinically- and cost-effective and it was subsequently recommended by NICE. MAT is about half the cost, so if it has a similar benefit it should be cost-effective.(3)

The pooled standard deviation (SD) in our pilot study was 14.5.(6) Allowing for the multicentre nature of this study along with the small size of the pilot, we have used the upper boundary of the 60% confidence interval to estimate the SD. According to the method of Chen et al, this was 16.4.(31) In this competency-based trial, each site will contribute small numbers and adjustment for clustering is not necessary. Hence, for a two-group parallel arm design, assuming 90% power and two-sided 5% significance this would require a sample size of 116. Allowing for 20% loss to follow-up, this would result in a **target recruitment number of 144**.

6.2 Planned recruitment rate

6.2.1 Recruitment and consent

We estimate recruitment of 12/year from the primary centre (UHCW) and 3-6/year from secondary centres reflecting their current practice. Other contributing countries will each recruit 8-12 cases/year based on our pilot data and caseload of the leading units in those countries. We have planned for two of the three countries to open, allowing mitigation for any unexpected difficulties in each country. With a staggered start of sites (1/month in the UK), we anticipate recruitment will take 28 months.

6.2.2 Stop-go criteria

The first 12 months of randomisation will act as an internal pilot, with a target of 43 randomised, based on staggered opening of sites over the first year. We will apply stop-go rules as detailed in table 5 below.

The criteria for time to intervention have been chosen to ensure that both groups have fully recovered before the two-year primary outcomes time point. A two-year primary outcome has been chosen for this reason. The between arm difference in time to intervention will be assessed at 18 months to give time to form a worthwhile assessment. The follow-up criterion will be assessed when the first 40 randomised participants have passed their 12-month follow-up window.

All criteria will be reviewed monthly at the TMG meetings from the start of study recruitment. If the study meets amber criteria, we will inform the TSC, review processes, look to open additional sites or amend trial processes, and review again in six months. If the red criteria are met, we will discuss whether to stop the trial with the TSC, who will review the criteria and make a recommendation.

	Red	Amber	Green
Trial recruitment	< 66%	66 to 100%	100%
Recruitment rate per site per month	< 0.33[a]	0.33 to <0.4[a]	≥ 0.4[a]
Number of sites opened	<8 sites total	8 to 11 UK plus 1 Int*	12 UK plus 2 Int*
Total number of participants recruited	< 28	28 to 42	43
Treatment started[b] (both arms pooled)	<60%	60% to <100%	100%
Between-arm median difference in time to intervention[b]	>12months	>6 to 12 months	≤6 months
Follow-up rate at 12 months post-randomisation[c]	<80%	80%-100%	100%

*Int = international recruitment.

[a]this figure is a mean across sites, individual sites will be very variable in recruitment due to current referral patterns (We have calculated recruitment to range from 1.2 – 0.25 per site per month depending on referral pattern for individual units or population served, the figure presented reflects the mean figure across all sites to achieve successful recruitment to target)

[b]these figures have been chosen to ensure that both groups have fully recovered before the primary outcomes timepoint, a 2-year primary outcome has been chosen to allow for some expected differential. As the red criteria is set at 12 months, the earliest that we will be able to judge these criteria will be the 18-month time point.

[C]the follow-up criterion will be assessed after the first 40 people have passed their 12-month follow-up window.

These criteria will all be monitored monthly at our Trial Management Group meetings to ensure any issues are acted upon promptly and as they arise.

Table 5: Stop Go Criteria

6.3 Statistical analysis of effectiveness and harms

A detailed statistical analysis plan will be written and agreed with the DMC prior to the primary analysis taking place. Data will be reported in line with the CONSORT guidelines.(32,33)

6.3.1 Statistics analysis plan

Treatment effects will be presented with appropriate 95% confidence intervals (where relevant), for all analyses. Tests will be two-sided and considered to provide evidence for a

statistically significant difference if p-values are less than 0.05 (5% significance level). All analyses will be conducted as intention to treat unless otherwise specified.

6.3.1.1 Summary of baseline data and flow of patients

Descriptive statistics will be constructed for baseline data to check for any characteristic differences between allocation groups.

Graphical summaries will also be created to aid interpretation of key results. A CONSORT chart illustrating participant flow throughout the study will also be produced.

6.3.1.2 Primary outcome analysis

A generalised linear model will be used to assess differences in the KOOS4 at 24 months post randomisation. As a minimum, adjustment terms for allocation, age and baseline score will be used. Variables found to be unbalanced at baseline may also be fitted, if judged appropriate. Where possible, a random effect for centre or country effects will also be used.

6.3.1.3 Secondary outcome analysis

Secondary outcomes will be analysed using a similar approach to the primary analysis where data type and distribution allows. Outcomes which are categorical in nature (e.g. patient global impression of change) will be analysed using proportional linear or logistic regression and subject to the same variable adjustments.

To assess the effects of treatment switching, we will also construct models to compare participants on an “as treated” basis. That is, compare outcomes for those who receive each treatment, regardless of allocated group.

6.3.1.4 Exploratory analyses

Exploratory models will be performed to assess the change from pre-intervention scores to the 24-month outcome. (52) This may include assessing the trajectory of recovery over time using latent growth models, assessing variables as prognostic or mediating factors.

6.3.2 Subgroup analyses

Pre-specified subgroup analyses will be performed for affected compartment (medial or lateral), age (30 or over/under 30) and gender.

6.4 Procedure(s) to account for missing or spurious data

It is likely that some data may not be available due to withdrawal of participants, lack of completion of individual data items or other reasons. Where possible these reasons for data ‘missingness’ will be ascertained and reported. The nature and pattern of the missingness will be considered, including whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities available in the statistical analysis software. Where possible, a consistent approach will be agreed and used for both analyses of efficacy and cost effectiveness.

If imputation is undertaken, the resulting imputed datasets will be analysed, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified.

6.5 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from a NHS and personal social services perspective, according to the recommendations of the NICE reference case.(28) Given multinational recruitment, we will consider inter-country healthcare differences in constructing our analysis plan.(28,29)

Health service contacts, made in connection with their treatments, will be recorded as part of the resource utilisation questionnaires at three, six, twelve, eighteen and twenty-four months. Time lost from work (paid/unpaid), will also be recorded. Participants will be encouraged to use an electronic or paper calendar to help recall this information at follow-up. Intervention and sequelae healthcare resource use will be costed using most recently available UK published national reference costs, reflated to a common year.(34,35)

Generic health-related quality-of-life will be assessed at baseline, four weeks, three, six, twelve, eighteen and twenty-four months using the EQ-5D-5L questionnaire. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis.(36) Using the trapezoidal rule, the area-under-the-curve of health status scores will be calculated, providing patient-level QALY estimates. Quality of life years (QALYs) will be estimated for the whole cohort, applying UK values.

If the level of missingness data is below 5%, complete case analysis will be conducted. If not, mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data. Complete case data or imputation sets will be used in bivariate analysis of costs and QALYs to generate incremental cost per QALY estimates and confidence intervals.(37-40) Findings will be analysed and visualised as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. The potential for heterogeneity of cost-effectiveness findings by country will be explored by fitting interaction terms to models, and if necessary performing country-specific analysis applying local costs to the complete clinical effectiveness data. A UK cohort-only analysis will be included within planned secondary analyses. If the pattern of costs and benefits is non-convergent or non-dominant at 24-months we will develop a decision analytic model, using our expertise in economic modelling in this field.(3,4,41)

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will sponsor the trial, although the lead contracting organisation is UHCW. The day-to-day running of the trial will be managed according to Warwick SOPs, with UHCW SOPs used for contracting and oversight issues.

7.2 Ethical approval

All ethical approval, will be sought in each participating country. The trial will be conducted in accordance with all relevant regulations and guidelines, in each participating country.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D capacity and capability is received by the co-ordinating team.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e. investigators, RECs, participants, NHS Trusts, trial registries, as appropriate.

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 sponsors will be notified of the end of the trial (whether the study ends at the planned time or prematurely).

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

7.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register and will be registered on trials.gov. A protocol paper will be published prior to completing recruitment.

7.4 Notification of serious breaches to GCP and/or trial protocol

A 'serious breach' is a breach which is likely to affect to a significant degree –

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

If a serious breach occurs:

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
  (a) the conditions and principles of GCP in connection with that trial; or
  (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. Clinical negligence indemnity will be carried by local trial sites outside of the UK. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

Month	By date	Activity	Milestones
Phase 1: Set up			
-5 - 0		Finalise Protocol HRA/REC submission	Submission to HRA/REC
1 - 6		Complete HRA approval Prepare trial materials and CRFs Prepare contracts and plan site-initiation	1st TSC/DMC HRA approval Final versions of all materials approved
Phase 2: internal pilot			
6 - 18		Start recruitment (staggered start of sites). Recruit 43 participants during internal pilot.	12 UK sites open and recruiting to target, international recruitment started 36 UK, 7 international participants recruited
		Assess against stop-go criteria (after 12 months recruitment) Decision on trial progression	Report to DMC, TSC and HTA
Phase 3: Main trial, Analysis & Dissemination			
18-34		Complete trial recruitment	144 participants recruited
58		Complete 24-month follow-up	All 24-month follow-up closed
58 - 66		Data cleaning (3 months) Complete Analysis (3 months) Final data review with DMC/TSC Complete monograph (2 months)	Present results to DMC & TSC Final monograph, and dissemination of results

Table 6: Trial Timetable and Milestones

7.7 Administration

The trial co-ordination will be based at WMS/WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff, co-investigators and PPI co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Facilities will be available for in-person or teleconference as required.

Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

Smaller team meetings consisting of the CI, Co-CI, TM, TC and SPM, and any other invited members will meet between the main TMG meetings when required.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC is shown on page 4.

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

The DMC will consist of a minimum of three independent researchers, one who is an appropriate clinician and one who is a statistician. The DMC will meet approximately every six months for the duration of the recruitment and follow-up, although they may choose to meet less frequently at certain stages of the trial, such as when the study is in follow-up.

The DMC will meet in a joint TSC and DMC meeting (unless quorate numbers for each can not be achieved, in which case they will be separated) and as a separate committtee will then meet regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC, as detailed in the DMC Charter. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 5.

DMC meetings will also be attended by the CI, Co-CI, TM, TC (all at the discretion of the DMC chair and only for non-confidential parts of the meeting) and the trial statistician(s). Observers will be allowed in open sessions at the discretion of the chair, but will not be allowed in closed sessions.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.11 Essential Documentation

A Trial Master File will be set up according to Warwick SOPs and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

This study is funded by the NIHR Health Technology Assessment Programme (NIHR131629) and the National Health and Medical Research Council. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

8. MONITORING, AUDIT AND INSPECTION

The study will be monitored by the Research and Development Department at UHCW as representatives of the lead Sponsor and by the Quality Assurance team at WCTU as representatives of the sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.

A trial monitoring plan will be developed and agreed by the TMG and TSC based on the trial risk assessment. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. This plan will be available from the trial coordination centre and will also be lodged with the sponsors. Assessment of fidelity of the interventions will be assessed using the process and fidelity measures documented in section 2.9.1.1.

Whilst the monitors work in the same institution as the CI and trial team (WCTU), they will act independently of the trial team in this role. Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CI, Co-CI or the TMG) will may be considered triggers for on-site monitoring visits. The sponsors will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits, and REC review, providing direct access to source data/documents as required. Monitoring will be performed by exploring the trial dataset or performing site visits, as defined in the trial monitoring plan.

Recruitment sites are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients' views have been critical in developing the study and will continue to be important in its delivery. Two PPI representatives are co-investigators, both had MAT previously and BM was in the pilot trial, she was allocated PKT but then had a MAT three years later. They have given critical insights into the experience of patients with this condition and their experience of the interventions we plan to test. They were particularly clear about the major impact of their pain and disability on their lives especially at such a young age when they expect to be mobile and active. They clearly described this as being physically, mentally and socially restricting. This understanding has had an important impact on the application. It has informed the importance of addressing this under-researched population who are disabled at a young age. It has also had an important influence on study design, including outcomes and the planned interventions.

Prior to the stage one application, we spoke to six people who have had MAT or had PKT in the pilot. Everybody agreed the study was important. They emphasised the importance of function (including work and sport) in the short- to medium-term as the most important outcomes, we will collect data on these, mental health was also seen as an essential outcome by multiple respondents. They would find both MAT and PKT acceptable, the importance of a comprehensive PKT package was also a common feature and they welcomed suggestions to strengthen the programme with more digital media.

In preparation for this stage two application (through a Research Design Service PPI grant to pay for participants time, according to INVOLVE criteria), we engaged with five more patients. This was to explore the study in depth and to review the planned outcome pack, which was posted to them the before we undertook interviews. They were very supportive of the study and all would be happy to complete the forms. They wanted to avoid repetition (hence we have limited the number of timepoints for IKDC) and all five preferred digital methods for completing outcome scores. We have established a plan for app-based data collection as well as traditional paper-based option to be used in this study. As with the initial PPI exercise, they emphasised the value of qualitative data collection in parallel, this has been a consistent feature of PPI interactions but was not in the brief, so we will explore other funding to include some qualitative data capture in parallel to the main study.

The PPI co-applicants will be integral to the team, will engage in trial management meetings and will contribute to trial processes, including dissemination of the findings. We have embedded PPI closely into previous studies and we will ensure the PPI members voices are clearly heard as equal members of the management group for the study. Two further patients will be invited to be members of the trial steering committee. Within the Warwick CTU Trauma and Orthopaedics team we have a PPI reference group who meet every six months, we will also keep them informed of study progress and use them for additional lay oversight.

All lay representatives will be supported by the trial team and Chief Investigators and will be remunerated according to NIHR guidelines (https://www.nihr.ac.uk/documents/payment-guidance-for-researchers-and-professionals/27392). Training courses and materials for PPI members will be offered to all PPI members, where they are available. The trial team will ensure all PPI members have adequate support and training.

10. DISSEMINATION AND PUBLICATION

10.1 Patients and public

Dissemination to patients and the public will be led in conjunction with our patient partners, who have been closely involved throughout the study development. Dissemination to trial participants will follow current HRA guidelines and Warwick SOP 22 on publication & dissemination (https://www.hra.nhs.uk/planning-and-improving-research/best-practice/publication-and-dissemination-research-findings/).

We will use lay summaries and infographics which will be sent to trial participants (participants permission for this will be obtained at baseline), trial hospitals, and published on our trial website, or in conjunction with the main publication, if journal policies allow. Trial participants will be informed of the results using lay summaries and infographics on publication of the primary outcome results, we will follow current Health Research Authority guidelines in delivering this. We will prepare articles in magazines such as Arthritis Today, patient focused websites such as patient.co.uk and utilise social media to report our findings. We will use press releases to alert the popular press in conjunction with our press officer. A trial website will be hosted by WCTU and used to promote study progress and trial publications.

10.2 Surgical and wider clinical community

We will register the trial with ISRCTN and clinicaltrials.gov prior to starting and will publish the trial protocol during the recruitment phase and will post results on the registry within 12 months of trial completion.

Key findings will be presented at national and international conferences, such as the British Orthopaedic Association and the American Academy of Orthopaedic Surgeons. Our PPI representatives will be invited to participate in the proposed conferences and meeting and with the support of the team present findings and experiences from a patient perspective.

The study monograph will be prepared by the trial management team and other collaborators within three months of study completion. We will simultaneously prepare a manuscript (or manuscripts, if the health economics is better reported separately) for a high impact peer-reviewed journal. Reporting of the interventions will conform to the TIDieR checklist (42) and both the monograph and main results paper will conform to the CONSORT statement. (32) These publications will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community and policy makers.

We will prepare concise summaries for NICE, CADTH (Canada), HTRG (Adelaide), **ASERNIP-S** – (Australian Safety and Efficacy Register of New Interventional Procedures -Surgical), **KCE** (Belgian Health Care Knowledge Centre), Belgium, and INAHTA.

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