REPPORT

RECURRENT PATELLAR DISLOCATION:
PERSONALISED THERAPY OR OPERATIVE TREATMENT?

PROTOCOL

REcurrent Patellar dislocation: Personalised therapy or OpeRative Treatment? (REPPORT)

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TRIAL SUMMARY

Table 1. Trial Summary

Trial Title	REcurrent Patellar dislocation: Personalised therapy or OpeRative Treatment?	
Internal ref. number (or short title)	REPPORT	
Trial Design	A multi-centre pragmatic, international, randomised controlled trial (RCT) of Personalised Knee Therapy (PKT) compared to surgery	
Trial Participants	People aged 16 or over with two or more patellar dislocations and closed growth plates.	
Planned sample size	276	
Follow-up	Primary outcome: 18-months after randomisation. Secondary timepoints: Six, 12, 18 and 24-months post randomisation.	
Planned Trial Period	From: 1st January 2023 To: 31st December 2027	
	Objectives	Outcomes
Primary	*Clinical Effectiveness:* To compare the clinical effectiveness of Personalised Knee Therapy versus patellofemoral surgical care at 18-months post randomisation. *Cost Effectiveness:* To compare the cost-effectiveness of Personalised Knee Therapy against patellofemoral surgical care from an NHS and personal social service (PSS) perspective.	Participant reported function at 18-months using the Knee Injury and Osteoarthritis Outcome 4-domain Score (KOOS4). Base-case within trial analysis of cost per quality-adjusted life-years (cost/QALY).
Secondary	To quantify and draw inferences on pain, function, instability, dislocations, health utility, social participation, resource use,	All assessed at six, 12, 18, and 24-months unless specified otherwise.

	occupational status, further surgery, and adverse events at six, 12, 18 and 24-months after randomisation.	• KOOS4 (secondary outcome at six, 12 and 24-months only) • The five individual KOOS domains (symptoms, pain, activities of daily living, sports, quality of life) • Norwich Patellar Instability (NPI) Score • Health-related quality of life (EQ-5D-5L) • Work or education status (time off, change to status) • Social activities (PROMIS Satisfaction with Social Roles and Activities 4a Short Form) • Satisfaction with treatment • Patient global impression of change (single item) • Patellar dislocation events • Adverse events including surgical complications • Further knee surgery (either arm) • Resource use
Process Measure	Days from randomisation to treatment initiation. Physiotherapy (PKT and post-operative rehabilitation) and surgical CRFs to assess intervention fidelity including information on: • Number of physiotherapy sessions offered and attended • Composition of physiotherapy attended Participant CRFs to assess intervention adherence, including information on number of physiotherapy sessions attended, at six, 12, 18 and 24 months post-randomisation.	

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
BASK	British Association for Surgery of the Knee
BOA	British Orthopaedic Association
BOAST	British Orthopaedic Association Standards for Trauma and Orthopaedics
BPFS	British Patellofemoral Society
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HEAP	Health Economic Analysis Plan
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomisation Controlled Trial Number
ITT	Intention to treat
KOOS4	Knee Injury and Osteoarthritis Outcome Score
MD	Mean Difference
MRC	Medical Research Council
MPFL	Medial Patellofemoral Ligament
NHS	National Health Service
NPI	Norwich Patellar Instability score

PGIC	Patients' Global Impression of Change scale
PI	Principal Investigator
PIPS	Patella Instability: Physiotherapy versus Surgery
PKT	Personalised Knee Therapy
PPI	Patient & Public Involvement
PSS	Personal and Social Service
QALY	Quality-adjusted life years
QoL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REPPORT	Recurrent Patellar dislocation: Personalised therapy or OpeRative Treatment?
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TM	Trial Manager
TMF	Trial Master File
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

1.1.1 What is the problem being addressed?

Recurrent dislocation and instability of the patella is a profoundly disabling condition mostly affecting adolescents and adults under 30 years of age.[1-3] Recurrent dislocations may persist for many decades causing pain, cartilage, and soft tissue injury.[4, 5] Those affected commonly develop patellofemoral joint osteoarthritis.[4, 5] This can lead to long-term disability and continuing requirement for health services.[6] There are around 5,500 new cases of recurrent dislocation each year in the UK, and around 2,000 in Australia.[3, 7, 8]

First-time (primary) patellar dislocation is usually treated without surgery. It affects up to 43 per 100,000 people with the incidence rate estimated to be 147 per 100,000 among young females.[7-9] A second (recurrent) dislocation happens in around 40% of people, with a first dislocation, within the first five years.[3, 10, 11] If a second dislocation occurs, ongoing restriction is highly likely and outcomes are poor.[10-13] Between dislocation episodes, those affected say their patella feels unstable and about to dislocate; this is known as instability.[14, 15] It often leads to activity modification and restriction as people try to avoid dislocations or instability.[14, 15] Recurrent dislocation and instability can render individuals incapable of continuing education, work and social or physical pursuits, with a major impact on quality of life.[3, 14, 16, 17]

The term recurrent patellar dislocation refers to two or more patellar dislocations. Recurrent patellar instability refers to two or more patellar dislocations plus persistent instability. For the rest of the protocol, we will use the term patellar instability.

Patellar instability may be managed with physiotherapy or surgery. However there is uncertainty as to which strategy is best.[18-20] The choice between the two treatment options is currently based on the opinion of the treating clinician supported by case series data which focus mainly on surgery with little evidence for non-operative interventions.[11, 19, 21, 22] Some clinicians believe that without surgery, dislocations and restriction will persist and may be worsened by a delay as structures around the knee could be damaged. Others believe that physiotherapy is effective and avoids the discomfort, risks, recovery period, and

cost of surgery.[11, 19] There is no evidence from RCTs to determine best practice in recurrent patellar dislocations or instability.

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 service?

As well as the impact on people's quality of life, and the potential long-term disability associated with recurrent patellar dislocation, the condition is also a burden on health services. In 2020, a collaborative study for the British Association for Surgery of the Knee (BASK) reported 3,639 cases from 45 Trusts over five years.[23] Extrapolated to the full NHS, the data suggest around 2,000 surgical cases are performed annually (costs around £5M). This is consistent with data in Australia (relative to population size), where between July 2019 and July 2020, 1,100 cases were performed with an average cost of AUS$6,500.[24] Surgeons who participated in the BASK collaborative study were also surveyed about the REPPORT trial and were strongly supportive. They reiterated the previous uncertainty regarding how to manage people with recurrent patellar dislocation on initial presentation. From this survey, 52 surgeons across 44 Trusts said that they would recruit to the REPPORT trial.

1.2 Existing knowledge and the need for a trial

1.2.1 Patella Instability: Physiotherapy versus Surgery (PIPS) – a feasibility study

In 2019, we completed a mixed-methods feasibility trial (Patellar Instability: Physiotherapy versus Surgery - PIPS) across three NHS sites comparing a bespoke personalised knee therapy intervention versus surgery with post-operative rehabilitation for patellar instability.[25] A major finding from the PIPS study concerned the attitudes of participants to the potential need for surgery if randomised to a non-operative intervention arm. Previous major trials comparing a treatment strategy that starts with physiotherapy compared to a treatment strategy that starts with surgery have observed a proportion of people in the physiotherapy arm subsequently undergoing surgery.[26-30]

In clinical practice, the decision to recommend non-surgical management would always be made with an acceptance of the potential for future surgery. This was clearly expressed by patients when we discussed the study with them in PPI trial design activities and in the PIPS feasibility study participant interviews. Even if a proportion of people subsequently have

delayed surgery, a decision to have physiotherapy at presentation may improve outcomes, prevent surgery for many others, and be cost-effective. Our PPI representatives felt that patients would accept Personalised Knee Therapy and invest in it as long as they knew that the option of surgery was available to them in the future if Personalised Knee Therapy was not successful. Equally, a decision to undertake physiotherapy could result in ongoing damage from the underlying pathology leading to worse eventual outcomes (even if surgery is subsequently performed). We will only understand this with a pragmatic trial in which the potential for subsequent surgery is accepted as part of the evaluation.

To determine the correct treatment decision for people presenting with patellar instability, the REPPORT trial needs to compare the decision to offer one of two treatment strategies, in which future surgery is an accepted part of real-life care and evaluate the outcome of that important decision.

1.2.2 Systematic Reviews

A 2015 Cochrane review aimed to assess the effects (benefits and harms) of operative versus non-operative interventions for treating people with patellar dislocation. It included five trials involving people with primary patellar dislocations (n=344). No trials were found examining people with recurrent dislocations.[19] An updated review (expected 2022) with revised searches (including instability)[31] identified 10 trials (n=536), although only one of these (the PIPS feasibility study) recruited patients with patellar instability whilst the remainder recruited patients with single episodes of dislocation.

This updated review reported that people managed with operative rather than non-operative interventions following patellar dislocation had a lower risk of recurrent dislocation at two to five years (Relative Risk (RR): 0.47; 95% confidence intervals (CI) 0.32 to 0.71) and at six to nine years (RR: 0.62; 95% CI: 0.41 to 0.92). However, there was no clear difference between the interventions when functional outcomes were measured at two to five years (mean difference (MD): 9.52; 95% CI: -2.17 to 21.22) or six to nine years (MD: -3.25; 95% CI: -10.61 to 4.11). There was a greater risk of adverse events for those who received operative compared to non-operative interventions during the initial two years (RR: 9.10; 95% CI: 3.06 to 27.07). The evidence was judged as very low quality due to serious risk of selection bias, imprecision, and attrition bias based on trials which were underpowered, with limitations in reporting.

Importantly, only one trial has investigated outcomes of operative versus non-operative interventions for people with recurrent patellar dislocation, this was our PIPS feasibility RCT.[25] The updated Cochrane review has reiterated the need for a sufficiently powered, robust, pragmatic RCT investigating the management of people with patellar instability.

A 2017 systematic review (updated searches 2022) of non-operative care in the management of patellar dislocation comprising of assessment, strengthening exercise prescription (hip and knee), and orthotics, found wide variation in treatments and outcomes.[11] There were few data on recurrent dislocations, and even after first-time dislocations, there was only poor-quality data, mostly case series. Some studies highlighted persisting disability despite non-operative care, even with no further dislocations.[17] The evidence also highlighted that whilst there was an emphasis on quadriceps (thigh muscles) strengthening exercises, there was limited provision of other exercises and non-operative care strategies which may offer benefit including flexibility exercises, glutei recruitment (buttock muscle activity) programmes or orthoses (external devices or braces). Whilst there has been promise in other knee rehabilitation interventions for a tailored intervention programme, such as grading recovery by identifying patient goals related to return to work and sporting pursuits, this has only been piloted in this population in our feasibility study.[25, 32, 33]

Reviews of operative management consistently recommend medial patellofemoral ligament (MPFL) reconstruction[18, 34, 35], consistent with national guidelines described below. A tibial tubercle osteotomy may be added where patella alta (a high kneecap) is present.[18, 36, 37] Other operative procedures such as trochleoplasty or rotational osteotomy are occasionally required for complex anatomical deformity, but these are relatively rare (less than 10% of the recurrent dislocation population). People with these rare anatomical deformities are typically very difficult to treat with therapy alone, and surgery has a different recovery and complication profile to the procedures used for the majority of people with recurrent dislocation.[38]

Case series have reported good outcomes for MPFL reconstruction, alone or combined with tibial tubercle osteotomy, although functional outcome scores do not return fully to normal.[34, 36, 37, 39]

Reported complication rates of MPFL reconstruction are 3-7% (including: infections, deep vein thrombosis, pulmonary embolism, reoperation) with re-dislocation rates of 2-5%. Tibial tubercle osteotomy has a complication rate of around 5%, but subsequent removal of screws is common (30-50%).[40]

1.3 Research question

For people presenting with recurrent patellar dislocation (two or more dislocations in the same knee), is an initial management strategy of Personalised Knee Therapy or an initial management strategy of surgery most effective at improving participant-reported function and which is the most cost-effective strategy?

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 Clinical Trials Unit (WCTU) Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with UK GDPR.

Participants will be randomised to an initial management strategy of either Personalised Knee Therapy or surgery. This is a major decision; therefore, potential participants will be provided with precise high-quality information and consent materials, both at the time of consent and throughout the duration of 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. This information will be collected on trial CRFs.

When two-year follow-up analyses are complete, we will inform participants of the findings of the study to help their future treatment decisions. Dissemination to trial participants will follow current HRA guidelines (https://www.hra.nhs.uk/planning-and-improvingresearch/best-practice/publication-and-dissemination-research-findings/). They will be informed of the results using lay summaries and infographics on publication of the primary outcome results.

1.5 CONSORT

The trial will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) statement.[41]

1.6 Assessment and management of risk

These intervention packages are both standard interventions, used in the NHS at present. Risks will be no different from those that occur in normal practice. Inevitably, there is some additional risk related to the surgery group over the Personalised Knee Therapy group as any operation has inherent risks, and the wait for surgery may be longer, but not beyond what is normal for NHS practice. A risk assessment will be performed according to Warwick SOPs 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 SOPs and careful adherence to the principles of Good Clinical Practice (GCP).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

REPPORT is a two parallel arms, multi-centre, pragmatic RCT designed to assess the clinical and cost-effectiveness of Personalised Knee Therapy compared to surgery.

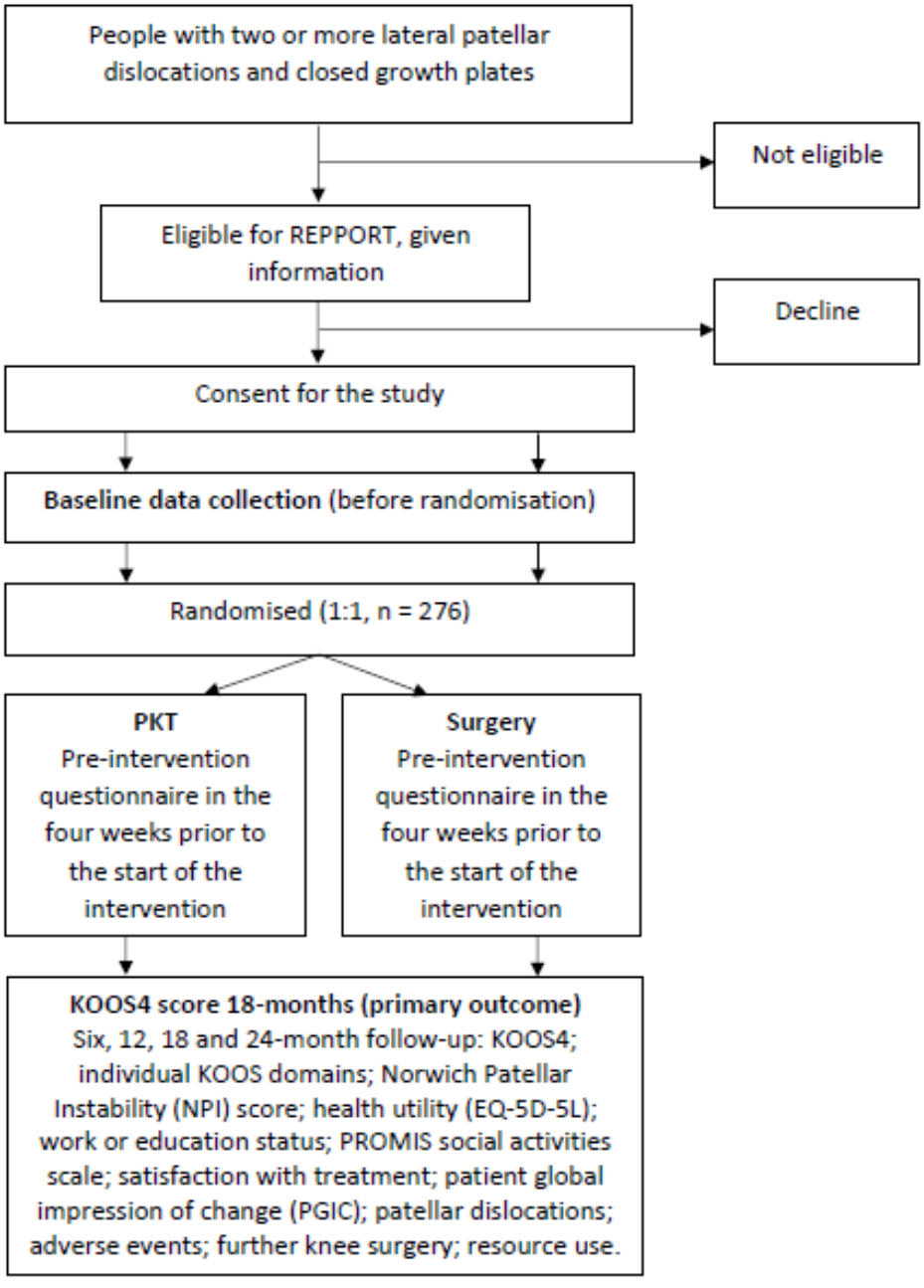

Figure 1. Trial Flow Diagram

2.2 Aims and objectives

The overarching aim is to determine whether an initial management strategy of Personalised Knee Therapy or surgical care is the most clinically effective and cost-effective approach for people with recurrent patellar dislocation (two or more dislocations in the same knee).

2.2.1 Primary objectives

1) To compare the clinical effectiveness of Personalised Knee Therapy versus surgery, based on participant reported function 18-months after randomisation, using the Knee Injury and Osteoarthritis Outcome 4-domain Score (KOOS4).
2) To compare the cost-effectiveness of Personalised Knee Therapy against surgery from an NHS and personal social service perspective.

2.2.2 Secondary objectives

1) To quantify and draw inferences on pain, function, instability, dislocations, health utility, social participation, resource use, occupational status, further surgery, and adverse events based on:
    - The KOOS4 at six, 12, and 24-months post randomisation.
    - The five individual KOOS domains (symptoms, pain, activities of daily living (ADLs), sports, quality of life) at six, 12, 18, and 24-months post randomisation.
    - The Norwich Patellar Instability (NPI) score at six, 12, 18, and 24-months post randomisation.
    - EQ-5D-5L at six, 12, 18, and 24-months post randomisation.
    - Work or education status at six, 12, 18, and 24-months post randomisation.
    - Social activities (PROMIS Satisfaction with Social Roles and Activities 4a Short Form) at 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 (PGIC) at six, 12, 18, and 24-months post randomisation.

- Number of patellar dislocations at six, 12, 18, and 24-months post randomisation.
- Adverse events including surgical complications at six, 12, 18, and 24-months post randomisation.
- Any knee surgery (either arm) at six, 12, 18, and 24-months post randomisation.
- Resource use at six, 12, 18, and 24-months post randomisation.

2) To evaluate process measures to compare days from randomisation to treatment initiation, and Personalised Knee Therapy and post-operative rehabilitation attendance and adherence.

2.3 Eligibility criteria

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

Inclusion criteria:

1. **Experienced at least two (self-reported) lateral patellar dislocations** affecting the same knee.
2. **Age 16 years or over at point of entry into the trial.**

If a participant has bilateral dislocations, the knee that will be included in the trial will be the one that is more problematic for the individual.

Exclusion criteria:

1. **Open growth plates on standard care imaging** (typically but not restricted to MRI). Surgery in the skeletally immature requires different surgical techniques and is beyond the scope of this trial.[42, 43]
2. **Presence of another knee condition which may cause instability** (e.g., cruciate ligament instability, unstable meniscal tear).
3. **Previous patellofemoral surgery**, except simple arthroscopy with/without lateral release.
4. **Severe trochlea dysplasia which in the opinion of the treating clinician requires trochleoplasty**.*

5. **Malalignment of femur or tibia requiring corrective osteotomy (not including tibial tubercle osteotomy).***
6. **Osteochondral/chondral injury requiring surgery.**
7. **Medial patellar dislocation.**
8. **Previous randomisation into the trial** (i.e., the other knee).
9. **Unable to have either physiotherapy or surgery.**
10. **Unable to adhere to trial protocols or completion of questionnaires** (the need to offer translations will be kept under review by the trial team).

* These are uncommon, <10% of the population, and challenging to treat.[18, 38, 44]

2.4 Participant identification/screening

Participants will be identified by clinical teams predominantly from orthopaedic departments and acute musculoskeletal services (such as injury review clinics). Depending on individual site contexts, we will also offer the option to recruit from emergency departments, intermediate care, or physiotherapy services. The flexibility in location to identify potential participants was identified as important from our feasibility trial.[25] We learnt that recruitment from tertiary surgical centres (i.e., specialist hospitals without emergency services) was more challenging, although this setting should not be excluded as it may be helpful in some centres. A high proportion of patients approached in the tertiary centre were ineligible due to complex problems. With this in mind, we will focus recruitment on secondary care centres and those clinics that receive referrals from the community or emergency departments.

We will actively advertise the trial amongst the knee surgeon community and encourage surgeons in non-trial sites to refer potential participants to trial sites.

Similar to the SUcceSS trial[45] we will use online and written advertising materials, social media communications and at conferences. This approach has led to substantially increased recruitment in SUcceSS (also a surgical trial) and we expect it to improve identification of the potentially 'lost' cases across the UK. Our study website, 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.

We will aim to recruit from at least 18 NHS hospitals across the UK (accepting that some sites cannot always take part as planned). The target for each site will be to recruit one participant per month. These include units with an established history of trial recruitment, and also units in regions with historical lower levels of orthopaedic research.

Eligibility will be assessed and confirmed by a clinician who is capable of doing so based on their current role, skills, and knowledge and is listed on the delegation log. Eligibility can be assessed by routine clinical evaluation, with no requirement for any specific investigation. Appropriateness for study eligibility will be recorded on a CRF.

Potential participants will be given verbal and written information about the trial and invited to discuss the trial with a suitably trained member of the research team. Depending on the trial processes at individual sites, information sheets may be posted or emailed to potential participants. However, information will be given as early after presentation as possible.[25] Individuals will be given adequate time to consider their participation (see 2.6.1. In-person consent). A member of the local research team will carry out the informed consent process (see 2.6. Informed consent), registration and baseline data collection.

Screening data will be entered directly on to the trial database (with any identifiers, except trial numbers, redacted for relevant database users). This will include details of the number of people presenting to recruiting clinical teams who are considered eligible, and the number who consent to enter the study. These data will be monitored at monthly Trial Management Group (TMG) meetings and used to populate the CONSORT statement in the trial report.

Recruitment training materials for trial staff developed for the feasibility trial will be adapted for use in this full trial.[46]

2.5 Site staff training

The trial coordination team will undertake site initiation visits (SIV) with local Principal Investigators (PIs) and all clinical and research team members. As well as giving an overview of the trial (key personnel, protocol, management, and oversight), the SIV is an opportunity

to provide training to those responsible for conducting trial related procedures including pathways to identify potential participants, confirming eligibility, obtaining consent, collecting baseline data, trial CRF completion, SAE reporting, withdrawals, screening log and data clarifications as well as performing interventions.

A training log will be used to document who has received training and this log will be held in the Investigator Site File (ISF). Research staff taking part in the trial 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 or leaves the research team or the local PI changes. Copies of delegation logs will be held securely at WCTU.

2.6 Informed consent

The local PI 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 suitably trained and delegated nominee will provide potential participants with both written and verbal information about what the trial entails. They will also answer any questions that the person may have concerning trial participation. Options for taking consent are listed below.

Recruitment will be open to people from 16 years of age (who meet the inclusion criteria). Our consent processes and information sheets/media have been carefully designed with assistance from our PPI representatives to ensure that all invited to participate in the trial are well-informed, and that those willing to participate provide informed consent.

It will be explained that entry into the trial 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 trial procedures at any time without giving reasons and without prejudice to any further treatment (see 2.8.2 Compliance/contamination/ adherence). The participant will also be free to discontinue trial treatment i.e., Personalised Knee Therapy or surgery, without giving a reason and subsequently continue in the trial for the purposes of collecting data.

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 the point that they lose capacity). If they regain capacity we will assume, unless they specifically withdraw it, that their previous consent stands, and will resume data collection activities.

If any new information arises during the course of the trial that may affect participants' willingness to continue in the trial they will be informed and, if applicable, renewed consent will be obtained using an amended consent form.

Participants' GPs will be informed by letter that they are taking part in this clinical trial.

We will monitor screening logs to assess for potential participants who are not fluent in written or spoken English and will make translations as necessary.

Trial procedures (i.e., those that occur after consent) including baseline assessments and randomisation will not be undertaken until written/signed informed consent (see 2.6.1) or witnessed remote verbal consent (see 2.6.2) has been given and appropriately recorded in the patient's medical notes.

2.6.1 In-person consent

Potential participants will be given study information and adequate time to consider participation before being invited to give their consent to become participants in the trial. The original Informed Consent Form (ICF) will be stored in the ISF with one copy given to the participant and one copy stored in the participant's clinical notes. We have not set a minimum or maximum time period for their decision as some people will wish to consent at the point that 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 is likely to be a number of weeks for Personalised Knee Therapy and could be several months for surgery.

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 trial, answer any questions and ascertain if the individual has decided to participate. If the potential participant agrees, they can complete and return the signed

consent form at the time (in a pre-paid envelope) or a follow-up visit can be arranged or witnessed verbal consent can be undertaken (see 2.6.2). If consent is returned by post or in person at a future date, a file note will be made to document this and explain why the clinician countersigned and participant signed dates differ on the form.

2.6.2 Witnessed remote verbal consent

Witnessed remote verbal consent is an option and will be obtained via telephone or any Trust approved online video consultation platform e.g., Microsoft Teams. The call/video call must be witnessed by a site staff member who will declare that consent was given appropriately, the trial explained fully, questions answered, and participants were given time given to decide.

Following remote verbal consent, a paper copy of the consent form will be signed by the clinician delegated to take consent and countersigned by the witness. A copy of the signed consent form will be given to the participant (via post, in person or electronically). 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.

2.7 Randomisation

2.7.1 Randomisation

Participants will be randomly allocated to the two treatment groups via a central computer-based randomisation system provided by the WCTU's programming team, independent of the study team. This will be performed after consent has been obtained and baseline data have been collected. This can happen on the same day as long as all processes occur pre-randomisation.

Randomisation will be in a 1:1 ratio using a minimisation procedure with a random factor of at least 70%, stratified by age group (<22/≥22), site of recruitment, and presence of patella alta in the study knee (defined by the presence of either a Biedert patella-trochlea overlap ratio <0.25 on cross sectional imaging or Caton-Deschamps >1.2 on lateral radiograph/other routine clinical imaging).[47-49]

Randomisation will be performed by any member of the local clinical or research team delegated to do so, using the online system. In the event that the online system is not working, sites should contact the study team on working days during working hours for guidance. As randomisation is not time critical in the REPPORT trial, waiting until the next working day is not a problem.

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

2.7.2 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 protocol until the end of the trial. Routine NHS datasets related to their care, for which they have consented (such as Hospital Episode Statistics) may be examined for adverse events (such as re-operations) unless they also specifically withdraw from this aspect of the trial on the withdrawal CRF or consent forms. The level of withdrawal i.e. discontinuing from trial treatment or complete withdrawal from the trial will be documented on a trial CRF.

Should a participant withdraw from the trial at any stage, they will be treated thereafter 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.

Needing to change the intervention for safety reasons after randomisation is not a reason for withdrawal. Participants may be withdrawn from the trial at the discretion of the CI and/or Trial Steering Committee (TSC) or Data Monitoring Committee (DMC) due to safety concerns. Participants would be kept in the trial and their data included in analysis under the intention to treat (ITT) 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 such a scenario they will be managed according to the best judgement of the treating clinician but will be kept in the trial for the purposes of data

collection on an ITT 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 able to have other treatments including other surgery as determined by their clinical team, although adherence to the allocated intervention will be encouraged where possible. Information about any additional treatment will be collected on follow-up CRFs.

2.8 Trial treatments/interventions

2.8.1 Trial treatments

A full summary of the Personalised Knee Therapy and surgical interventions will be available in the REPPORT manuals, prepared following surgical and non-surgical consensus meetings to which co-investigators and relevant staff from participating sites will be invited. The appropriate manuals will be made available on the REPPORT trial webpage for ease of access for participants randomised to respective allocation groups and sites.

2.8.1.1 Personalised Knee Therapy (PKT)

The Personalised Knee Therapy programme is an optimised package of non-operative care for patellar instability. We will use the Personalised Knee Therapy programme developed for the PIPS feasibility trial[25] (to which adherence was good).

PKT aim: A tailored programme aimed at each participant's individual needs and goals. This is likely to include reducing pain and swelling, optimising knee range of motion, and improving lower limb strength and function with the over-arching aim of functional restoration to activities meaningful to the participant i.e., work, college/education, sports, and recreational pursuits.

Delivered by: A qualified physiotherapist experienced in the management of knee problems and trained in the REPPORT PKT intervention (a PKT manual will be provided to all therapists). If possible, this should be the same physiotherapist for each participant for the duration of the programme. If a change of physiotherapists is needed e.g., to cover sickness or maternity leave, then a full formal handover should be performed and further REPPORT intervention training may be necessary.

Mode of delivery: The intervention will be personalised to the participant. 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 incorporating up to six sessions. There are additional options to either discharge the participant earlier if they have achieved their goals or extend their treatment 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.

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

Documentation: Initial assessment and treatment interventions will be recorded using a Personalised Knee Therapy CRF. A copy of this may be used for the physiotherapist's departmental notes but only once agreed by their service lead as appropriate to do so.

Potential treatments:

- Education and advice
- Exercise individually prescribed from a core template including muscle strength (frequently quadriceps complex) and recruitment (frequently glutei complex) exercises, flexibility (frequently hamstring complex, iliopsoas, gastrocnemius) exercises, and proprioceptive exercises
- Analgesia
- Activity advice with graduated exposure to activities which individuals identify as perceived threats for recurrent dislocation
- Non-weightbearing
- Patellar stabilising orthoses and braces
- Electrostimulation
- Exercise/group gym classes
- Manual therapy

- Cognitive behavioural approaches

Exercises will be individually prescribed from a core template of exercises. The programme will be supervised by a physiotherapist, and then practised at home with a comprehensive home rehabilitation plan. This will be supported, and adherence promoted, with a treatment booklet providing guidance on exercises prescribed and general recovery advice, using paper, web based or MyRecovery patient App (https://www.msk.ai/patients) materials.

Phases of treatment: The PKT programme has three phases.[25] These are framed on functional progression, based on objective criteria with an early, middle, and later phase of treatment.

- Progression from early to middle phases required the person to have good range of motion and quadriceps strength with minimum pain.
- Progression from middle to later phase (return to sport and higher-level function) required the person to have good proximal muscle control with rotational stability on multi-directional activities.
- People who experienced instability symptoms or recurrent dislocation were required to return to an earlier phase.

Site training will be provided to all physiotherapists delivering the intervention to promote fidelity to the programme. This will occur prior to sites opening and where possible, in alignment with site initiation visits. Training will be delivered by the central trial team.

As with surgery, the time from randomisation to the start of the Personalised Knee Therapy intervention (first physiotherapy contact) will be recorded. Reporting of both interventions will conform to the TIDieR checklist.[50]

2.8.1.2 Surgery

Surgery will be performed according to published British Orthopaedic Association Standards for Trauma and Orthopaedics (BOAST) guidelines.[20, 51] These will be refined into a trial document covering core operative principles and post-operative management by a working group comprising surgeons, patients, physiotherapists and other key stakeholders as determined by the group.

Based on established guidance and current reviews, the most widely recommended surgical treatment is MPFL reconstruction, a relatively simple procedure in which the gracilis or semitendinosus tendon is harvested and attached between the patella and the femur, using a screw in the femur. This typically involves three incisions of around 3cm each, complications are infrequent (approximately 3-5%) and re-dislocation rates are between 2% and 5%.[34, 36, 37, 39]

People with patella alta (approximately 30-50% of the recurrent dislocation population)[52] may also undergo a simultaneous tibial tubercle osteotomy, a procedure in which the bony attachment of the patella tendon is cut and moved, usually by around 1cm. This involves an incision of about 8cm and would typically be performed with a MPFL reconstruction simultaneously. The screws used to fix this may need removal at a later time.

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 will be assessed using a CRF which will include details of surgery (surgical procedure, surgical findings, theatre time, tourniquet time, any other procedures).

In the feasibility trial, mean time to surgery was 16 weeks, although we have allowed longer for this in the design given COVID related uncertainty in clinical service provision. Recovery after surgery would expect to plateau by around six months.[53]

Rehabilitation for the surgery group will be according to a programme based on the minimum standard of care consistent with normal NHS practice, as used in the feasibility trial. This will ensure that the physiotherapy intervention can be clearly described at the end of the trial and prevent care that falls below usual accepted practice.

The rehabilitation programme will aim to start within the first three weeks after surgery and is lower-limb exercise-based with the aim of maximising post-operative recovery and functional restoration during the post-operative healing period.

There is no evidence that physiotherapy prior to patellofemoral surgery improves outcome. It may risk reducing adherence to the post-operative programme, so Personalised Knee Therapy will not be used prior to surgery.

2.8.2 Compliance/contamination/adherence

Attendance to no physiotherapy visits will be considered non-compliance with either Personalised Knee Therapy or post-operative rehabilitation. Attendance to less than three sessions of Personalised Knee Therapy will be considered as partial compliance. However, in some instances the treating physiotherapist and participant may agree that all treatment goals have been met early and therefore, the participant could be discharged after two sessions, for example. This detail will be recorded on the Personalised Knee Therapy CRF.

Participants randomised to surgery will be considered non-compliant if the operation does not occur. They will be partially compliant if they have the operation but no post-operative rehabilitation and fully compliant if they have their surgery and one or more post-operative rehab sessions. Further details are outlined in section 3.1.1.3 Process and fidelity measures.

2.9 Blinding

Due to the nature of the interventions, Personalised Knee Therapy versus surgery, blinding of participants and practitioners is not possible and, therefore, will not be performed. Allocation concealment will be maintained by ensuring all baseline data are collected prior to randomisation and the use of an independent randomisation system.

2.10 Co-enrolment into other trials

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

2.11 End of trial

The trial will end when analysis of 24 month follow-up data is completed, although this will be extended if funding is received for five- or ten-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 or Sponsor.

- Following recommendations from the DMC or 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 (REC) 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 team member consultation and interaction with our experienced clinical team to ensure we have chosen appropriate measures and a timeframe that captures the important variables without placing too much burden on participants. Our PPI group reviewed the planned questionnaire packs which included the proposed primary and secondary outcome measures. They reported taking between 12 to 15 minutes to complete the pack and this was “acceptable”.

Our patient partners have particularly emphasised the importance of occupational, sporting, and social outcomes as well as more established pain and function measures. We have piloted our outcome set with our PPI representatives who agreed they were appropriate to their problem and were not an excessive burden.

3.1.1.1 Primary outcome

- The four domain **Knee Osteoarthritis Outcome Score (KOOS4)** score 18-months after randomisation.

This is a 25-item knee-specific instrument (0-100, 100 best score) which sums four of the five domains of the full KOOS score (the domains for symptoms, pain, function/sports and quality of life, but not activities of daily living).[54] It has been widely used in previous trials in knee surgery, including young adult non-arthritic populations such as this one, placing this trial in the context of the wider knee surgery literature.[27, 29, 30, 55, 56] It has been shown to be responsive to change in both surgical and non-surgical intervention trials.[57]

Knee-specific function assessed by KOOS4 has been selected over the single domain of instability tested by the Norwich Patellar Instability (NPI) score used in the PIPS feasibility trial.[25] This decision is supported by our PPI group who placed function higher in importance than dislocation events.

Whilst the NPI score is a valid and reliable tool to assess perceived patellar instability, by virtue of its scoring method, only activities which participants engage in are scored.

Consequentially it has demonstrated a floor-effect.[15] The NPI score has been predominantly used when research has included a primary end-point of 12 months. Given the proposed trial's endpoints are 18 and 24-months, discriminating outcomes between the groups for those who have better outcomes at 24-months may be more challenging if the NPI score was the primary outcome.

Surgery provides a physical restraint to instability but if it causes pain or stiffness, it may not improve overall function. Our recent update to the current Cochrane review is consistent with a view that surgery may reduce further dislocations, but functional outcomes are much more uncertain.[19, 31] Physiotherapy may give functional benefits whilst still leaving some residual instability. For one treatment to be recommended over another, the higher order of physical function is of greater importance to patients and the contribution from our PPI representatives confirms that this is the most important primary outcome for the trial.

3.1.1.2 Secondary Outcomes

- KOOS4 at baseline, pre-intervention, six, 12, and 24-months.
- The five individual KOOS domains (symptoms, pain, activities of daily living, sports, quality of life)[54, 58] at baseline, six, 12, 18, and 24-months post randomisation. The KOOS5 is a validated knee specific instrument developed to assess the patients' opinion about their knee and associated problems.
- NPI score[15] at baseline, six, 12, 18, and 24-months post-randomisation.
- Health utility (EQ-5D-5L)[59, 60] at baseline, pre-intervention, six, 12, 18, and 24-months post-randomisation. The EQ-5D-5L is a validated measure of health status 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.
- Work or education status (time off, change to status) at baseline, six, 12, 18, and 24-months post randomisation.
- Satisfaction with social roles (PROMIS scale)[61] at baseline, six, 12, 18, and 24-months post randomisation.

- Satisfaction with treatment[62] at six, 12, 18, and 24-months post-randomisation using a 5-point Likert scale.
- Patient global impression of change (PGIC) scale (single item)[63] at six, 12, 18, and 24-months post-randomisation. This is a simple 7-point scale assessing perception of improvement.
- Patellar dislocations at baseline, six, 12, 18, and 24-months post-randomisation
- Adverse events including surgical complications at six, 12, 18, and 24-months post-randomisation (see section 4).
- Further knee surgery (either arm) at six, 12, 18, and 24-months post-randomisation.
- Resources used by interventions and assessed at six, 12, 18, and 24-months post-randomisation.

As there may be a differential wait for the intervention between arms, we will collect KOOS4 and EQ-5D-5L within four weeks before the start of intervention (both arms).

We will minimise missing data utilising experience from the feasibility trial, including paper and app-based solutions, telephone and text reminders, multiple contact details, clinical follow-up, and vouchers with the 18-month follow-up invitation.[25]

We will consent for extended follow-up and linkage to routinely collected datasets. We will apply for funds for five- and 10-year follow-up, including NHS Digital data, to evaluate longitudinal change and further intervention (such as further surgery), to feed into future economic models. Participants will be consented for this at baseline.

Other data collected at baseline will include age, sex, BMI, previous treatment, age at first dislocation and cause (trauma/non-trauma), Beighton score for hypermobility, analgesia, expectation, and work/education status, as well as equality and diversity measures (see next section).

3.1.1.3 Process and fidelity measures

- Days from randomisation to treatment initiation.
- Physiotherapy (PKT and post-operative rehabilitation) and surgical CRFs to assess intervention fidelity including information on:
    - Number of physiotherapy sessions offered and attended
    - Composition of physiotherapy

- Participant CRFs to assess intervention adherence, including information on number of physiotherapy sessions attended, at six, 12, 18 and 24 months post-randomisation.

3.1.2 Equality, Diversity, and Inclusion

It is important that we ensure that all potential participants have the same opportunity to take part. We have carefully addressed this in our choice of sites and in our recruitment and trial processes to ensure all eligible patients who present are informed about the trial. As part of baseline data capture, we will collect equality and diversity measures to assess if the trial population is representative of the population of interest. Specifically, we will collect data on age; disability; gender reassignment; marriage and civil partnership; pregnancy and maternity; ethnicity; religion or belief; sex; sexual orientation; socioeconomic status (based on postcode district).

We will monitor reasons for exclusion on CONSORT charts at monthly TMG meetings and address any potential issues as they arise.

We will support participants during their research journey, monitoring for any reasons that they may be finding it hard to engage in study processes. We will include costs for clinical follow-up at 12 and 18-months to ensure people have access to their healthcare teams and to help with outcome collection.

3.1.3 Safety

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

3.1.4 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.[64] Bespoke resource utilisation questionnaires will be developed to meet the specific needs of the trial. Health service and social service contacts, made in connection with participant's treatments will be recorded as part of the resource utilisation questionnaires. Time lost from work (paid/unpaid), will also be recorded. A detailed Health Economic Analysis Plan (HEAP) will be developed.

3.2 Schedule of delivery of intervention and data collection

Table 2. 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 (to be collected within 4 weeks before intervention starts)	Intervention	Medical note review	6-month follow-up	12-month follow-up	18-month follow-up	24-month follow-up
Time after randomisation (±window)	-	0		Data within 4 weeks of completion of allocated treatment	As required from randomisation to 24 months	6 months (-6w/+3m)	12 months (±3m)	18 months (±3m)	24 months (-3/+6m)
Check eligibility [$]	✓								
Invitation to study [$]	✓								
Informed consent [$]		✓							
Medical history [$]		✓							
Inclusion/exclusion criteria [$]		✓							
Randomisation [$]		✓							
Intervention (PKT/ surgery & post op physio) [$]				✓					
Adverse events [$]					✓				
Patellar dislocations and further surgery [$]					✓				
Rehabilitation attendance [$]					✓				
KOOS4 [#]			✓						
KOOS [#]		✓				✓	✓	✓	✓
NPI [#]		✓				✓	✓	✓	✓

EQ-5D-5L [#]		✓	✓			✓	✓	✓	✓
Work or education status [#]		✓				✓	✓	✓	✓
PROMIS satisfaction with social roles [#]		✓				✓	✓	✓	✓
Satisfaction with treatment [#]						✓	✓	✓	✓
Social activities [#]						✓	✓	✓	✓
PGIC[#]						✓	✓	✓	✓
Problems and complications [#]						✓	✓	✓	✓
Health resource use [#]						✓	✓	✓	✓
Painkiller use [#]						✓	✓	✓	✓

[$] site completed

[#] participant completed

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events

An Adverse Event (AE) in this study will be defined 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 trial, and to avoid unnecessary recording of events, we will only collect AEs or Serious Adverse events (SAEs) related to their treated knee and to the treatment they receive in the trial (or any treatment for their treated knee) or related to trial processes.

4.1.2 Recording adverse events

AEs related to the surgical procedure including the surgery, anaesthetic, post-operative care and rehabilitation, any component of the Personalised Knee Therapy package, or any knee treatment in the AE reporting period will be recorded on the appropriate CRF for return to the trial central office and reported to the relevant oversight committees.

AEs related to the treated knee, treatment received in the trial (or any treatment for their treated knee) or related to trial processes 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 as AEs or SAEs unless in the opinion of the clinical team, they are untoward, excessive, or outside of what might normally be expected for the procedure. These 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 six months (note that pain after six 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.
- Ongoing instability symptoms.

All recorded AEs 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 (SAE) is an AE, as defined for this trial (see 4.1.1), 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.

For the purposes of this trial, as with AEs, we will only collect SAEs related to the participant's treated knee, to the treatment they receive in the trial (or any treatment for their knee) or related to trial processes.

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 repport@warwick.ac.uk and the wctuqu@warwick.ac.uk resource account in the first instance.

All **SAEs** that meet the reporting criteria for this trial (see section 4.1.2 and 4.1.3) 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, repport@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 (TM) 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 PI's and CI's 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, SAEs will only be reported where there is an untoward medical occurrence in a participant related to their treated knee and to the treatment they receive in the trial (or any treatment for the knee) or related to trial processes. Other events that do not meet this definition will not be reported. Normal events defined in section 4.1.2 will not be reported as AEs or SAEs.

4.1.6 Assessment of Causality

A clinically qualified member of site 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 trial 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 descriptions in Table 3.

Table 3. SAE causality

Relationship to trial intervention	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 occurred 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.

4.1.7 Assessment of Expectedness

Where reported, SAEs will be assessed for having a possible causal relationship with the intervention or its associated procedures. Where a causal relationship is established an evaluation of expectedness will be made by the CI or their delegate, using the list below. 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.
- Nerve or vessel injury due to local anaesthetic (i.e., local blocks or spinal anaesthetic).
- Spinal haematoma.
- Stroke or Cardiac Event.
- Death.

Those related to the operation itself:

- Exacerbation/persistence of knee pain or instability 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 or surgical 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.

- Revision surgery or other corrective surgery.
- Irritation from metalwork or surgery to remove metalwork.
- Thrombosis (deep vein thrombosis, pulmonary embolus, cerebral infarct).
- Damage to nerves or vessels.

Those related to physiotherapy (post-surgical rehabilitation or Personalised Knee Therapy):

- Persistent muscle soreness or muscle injury.
- Bruising.
- Swelling.
- Skin damage (for example, from bracing).
- Exercise-related fatigue.

Treatments of expected events listed above (such as surgery for infection or wound problems) are also expected events.

If the SAE is not listed above, and is considered to have at least a possible causal relationship to the intervention, the event would therefore be classified as unexpected and will be reported to the REC within 15 days.

4.2 Responsibilities

Principal Investigator (PI) (or delegated clinician):

- Checking for AEs when participants attend for treatment/follow-up.
- Using medical judgement in assigning seriousness and causality.
- Ensuring that all SAEs (according to the trial criteria) 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 trial team at WCTU in line with the requirements of the protocol and Warwick SOPs.

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 causality and expectedness.
- Timely 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 (TMP).
- Production and submission of annual reports to the relevant REC.
- Monthly review of accumulated AEs/SAEs at TMG meetings.

Sponsor (University of Warwick):

- 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 TMP.
- 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 TMP.
- 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 TSC Charter, periodically reviewing safety data (without reference to allocation) and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

- In accordance with the DMC Charter, periodically reviewing safety data, overall and by allocation group 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 where there may be a relationship between the trial interventions or the condition being studied (in this case, any knee condition, or an event related to the anaesthetic, surgery, hospital admission, physiotherapy) 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 and the manufacturer) 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 three 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

All processes related to data management will be detailed in the Data Management Plan (DMP).

Personal data collected during the trial will be handled and stored in accordance with the UK General Data Protection Regulation (UK GDPR).

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 trial at the end of the trial and for long-term follow-up if funding is secured. 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 SOPs (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 SOPs (SOP 35).

5.1 Data collection and management

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

The CRFs will be developed by the TM in consultation with the CI, 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 if screening data reveals that language barriers are affecting participation and a predominant language, or languages, can be identified.

Participants will be given the option to use an App or website page for follow-up data collection when they consent to join the trial. Postal forms will still be used for those who prefer them, or for non-responders. The use of digital means for data collection, such as an app, was preferred to paper forms by all patients who we have discussed this with. This should improve the response rate and participant experience in this trial.

We have a quote for delivery of a study app from a UK company with an established digital platform for data collection in orthopaedic patients (Future Health Works; myrecovery.ai). We have worked with them successfully to develop apps for multiple studies in our unit

using the same platform, (ARTISAN, NIHR HTA; RACER, NIHR HTA; METRO NIHR DRF). The company already have permissions to use the measures (including EQ-5D-5L), they have completed independent data security checks, and have full approval from the University of Warwick's Information Technology department for the platform to be used for data collection in clinical trials.

Participants may be invited for clinical follow-up at 12 and 18-months. If the central team at Warwick CTU is having or anticipates (based on previous follow-ups) difficulties collecting the primary outcome data at 18 months via app, post or telephone from an individual, the central team will contact the site research teams to ask if they can invite the participant in to site for a clinical follow up to collect this data. This clinical follow up is normal care in some centres and additional in others, therefore, we have costed for these visits in the SoECAT. There may also be additional costs for translators.

All participants will be given a £30 gift voucher at the 18-month follow-up timepoint, which would remunerate any travel costs for this. In the pilot, a clinical follow-up helped support collection of outcome data, especially for people who lack confidence in written English where a member of the site research team can support them in completing questionnaires. Additionally, this strengthens the inclusivity of the trial.

Reminders will be sent via text messaging, post or by email to improve response rate.[65, 66] Our PPI feedback was positive about this as a way of reminding people. As is typical for our unit, we will take multiple contact details, including next of kin, (which will be stored securely in the trial database/MyRecovery App, to ensure a high response rate. Participants will only provide next of kin details where they have prior permission to do so. Where people do not respond (with prior consent), we will write to their GP to request information on potential complications or re-operations or from routine datasets, to ensure we do not miss critical safety data.

5.2 Database

The database will be developed by the Programming Team at WCTU and a full specification (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 WCTU 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 trial, and/or WCTU. Electronic data will be stored on password protected university computers in a restricted access building. Data (including personal data) will be removed from the MyRecovery records once we have completed the final follow up of the final participant.

5.4 Data access and quality assurance

All data collected will be de-identified after the collection of the baseline demographic data for each participant, except where this is not possible such as contact details for follow-up, in which case it will be kept separately.

Confidentiality will be strictly maintained, and names or addresses will not be disclosed to anyone other than the staff involved in trial follow-up. Participants will be identified by ID number, initials, and age only where necessary. Any identifiable participant data on paper 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 REC.

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 trial 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 10 years without investigator support. A data dictionary will be produced. 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 REPPORT TMG and WCTU data sharing committee. 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 REPPORT TMG.

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

After one 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 10 years after completion of the trial.

6 STATISTICAL ANALYSIS

6.1 Power and sample size

Following methods outlined by Chen at al.[67] we performed a scoping review of papers reporting KOOS4 in patellar dislocation. This identified 10 studies (non-surgical and surgical treatment) from which the 80th centile of the standard deviation (SD) was determined to give a conservative estimate of 21 for the SD. Based on the feasibility study and data from other orthopaedic studies within our unit, we assume that follow-up data are correlated with those collected at baseline (within person similarity). We conservatively estimate the correlation coefficient (ρ) as 0.5 for the KOOS4 at 18-months follow up. By explicitly including this adjustment in the sample size calculation, we reduce the effective SD from 21 to 18.2

We anticipate that there will be treatment switching between allocation groups in this pragmatic design. Hence, the choice of target difference should reflect any potential dilution of the observed treatment effect in the primary intention to treat (ITT) analysis. Therefore, reducing the between group target difference in KOOS4 score from 10 to 8-points (an effect size of 0.44) represents an important worthwhile difference for this design and population.

For a two-group parallel arm design, 90% power and 5% significance, we require data on 110 participants in each group. Allowing for an anticipated 20% loss to follow-up **results in a target sample size of 276 participants**. In this competency-based trial, each site will contribute small numbers and inflation for clustering is not necessary.

6.2 Planned recruitment rate

We estimate recruitment of 12 participants per year from the primary centre and four high recruiting centres, and six to nine participants per year from other centres, reflecting our feasibility experience. Based on 16 to 20 UK sites with a staggered start of two sites/month, recruitment will take 24 months. We have based recruitment rates on current practice but expect this strategy to improve recruitment beyond this.

6.2.1 Stop-go criteria

The first nine months of randomisation will act as an internal pilot, with a green target of 61 randomised, based on staggered opening of sites over the first year of recruitment (Table 4).

We will apply stop-go rules with the same percentage thresholds as used for ARTISAN and RACER-Knee (NIHR HTA 13/84/10 & 128768). In addition, thresholds for adherence with Personalised Knee Therapy and between-group time to intervention (randomisation to either first physiotherapist consultation for Personalised Knee Therapy or surgery) will be set. We have included a criterion for crossover to monitor the potential impact of this on our sample. The criterion for time to intervention has been chosen to ensure that both groups have fully recovered before the 18-month primary outcomes time-point.

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, particularly reflecting the nature that crossover may occur at any point post-randomisation. If the red criteria are met, we will discuss stopping the trial with the TSC and funders.

Table 4. Stop Go Criteria

	Red	Amber	Green
% Threshold			
Trial recruitment	< 66%	≥ 66%	≥ 100%
Recruitment rate/site/month[a]	< 0.5a	0.5 – 0.75a	≥ 0.75a
Number of sites opened	< 8 sites total	8 – 16 sites	16 sites
Total number of participants recruited	< 40	40 - 61	= 61
Non-adherence with Personalised Knee Therapy[b] planned sessions	>30%	1 - 30%	0%
Surgery date within 12-months of randomisation[b]	<70%	70 - 99%	100%
Crossover by 12-months[b]	20%	0 – 20%	0%

[a]This figure is a mean (x) across sites, individual sites will be variable in recruitment due to current referral patterns (Range 1.2-0.25 per site per month). [b]These criteria will formally be assessed when the internal pilot participants have completed the 12-month time point but will be monitored monthly across the study so that early problems can be identified and addressed.

6.3 Statistical analysis of effectiveness and harms

A detailed Statistical Analysis Plan (SAP) will be written by trial statisticians in line with Warwick SOP 21. The final version will be shared with the CI, the TSC and the DMC prior to the primary analysis taking place. The final analysis report will be reported in line with the CONSORT guidelines.[41, 68]

6.3.1 Statistical analysis principles

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 following the ITT principle unless specified otherwise.

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 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

The primary outcome will be analysed on an ITT basis and in line with the superiority design of the study. The primary model will be a generalised linear model used to assess differences in the KOOS4 score between treatment groups at 18-months post randomisation. At a minimum the model will include terms for allocation, age, sex, recruitment site, presence of patella alta and baseline KOOS4 score. If other important baseline variables are identified, they may be fitted as appropriate. Fitting a random effect for site effects will also be explored.

6.3.1.3 Secondary outcome analysis

Secondary outcomes will be analysed using a similar approach as appropriate to data and distribution. Categorical outcomes will be analysed with similar structure of models but with proportional logistic regression models.

6.3.1.4 Subgroup analyses

Pre-specified sub-group analyses will be undertaken to explore whether the intervention effect differs between:

- Age group (<22 or ≥22)
- Presence of patella alta (yes/no)

The subgroup analyses will follow the methods described for the primary analysis, with additional interaction terms incorporated into the mixed-effects regression model to assess the level of support for these hypotheses.

The study is not powered to formally test these hypotheses, so they will be reported as exploratory analyses only, and as subsidiary to the analysis reporting the main effects of the intervention in the full study population.

6.3.1.5 Sensitivity analyses

The primary inferences will be drawn from the models outlined under the ITT principle for the trial intervention of the *initial treatment strategy*. However, treatment switching is an important consideration in this study and other analysis populations will be used for exploratory analysis. An "as-treated" population, defined by the actual treatment received (i.e., those who underwent surgery and those who adhered to Personalised Knee Therapy) will be conducted. Per protocol analysis, restricted only to participants who adhere to protocolised treatment, will also be conducted to assess impact of protocol non-adherence. More details are given in the SAP.

The results of any exploratory analysis in non-ITT populations will be interpreted with caution because bias from confounding can be introduced by moving participants from their randomised group.[69]

6.3.1.6 Exploratory analyses

Exploratory models will be investigated to assess the change from pre-intervention scores to the 18-month outcome. This may include the use of latent growth models to assess trajectories of recovery.

6.4 Procedures to account for missing or spurious data

Missing data will be scrutinised and where possible, the reason for missingness recorded. If appropriate, multiple imputation methods in statistical software will be used. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Consistency between cost-effectiveness and clinical effectiveness models will be explored and implemented where appropriate.

The results of the primary outcome model will not include the use of imputed datasets, but a sensitivity analysis using fully imputed datasets would be considered as an appropriate sensitivity analysis in comparison with the primary outcome model.

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.[70] Details of the prospective plan and analysis will be described in the Health Economics Analysis Plan (HEAP) written by the trial health economists in line with guidance from Warwick SOP 21.

Health service contacts, made in connection with their treatments at six, 12, 18, and 24-months, will be recorded as part of the resource utilisation questionnaires. Time lost from school, college, university, or 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 recorded and costed using most recently available UK published national reference costs, reflated to a common year.[71, 72]

Generic HRQoL will be assessed at baseline, three, six, 12, 18 and 24 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.[73] 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 missingness of patient-level costs or QALYs ≤ 5%, the primary analysis will use complete case data.[74] If missingness exceeds 5%, 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 analyses of costs and QALYs to generate within trial incremental cost per QALY estimates and confidence intervals.[75-78] Findings will be analysed and visualised as cost-effectiveness acceptability curves, net monetary benefit, and value of information analysis. Pre-specified sensitivity analysis will be used to explore the robustness and generalisability of findings.

The within trial analysis will serve as the primary analysis under several conditions reflected in the pattern of incremental costs and QALYs over the 24-months of follow-up: if these converge (no longer-term difference between interventions) or if they diverge such that either Personalised Knee Therapy or surgery are clearly dominant (with further extrapolation uninformative). If further modelling is likely to be informative, then the modelled finding will form the primary analysis. We will develop a decision analytic model, using our expertise in economic modelling in knee surgery.[79-81] The probabilistic model is likely take the form of a Markov model, capturing subsequent surgery including primary and revision knee replacement over the life course, with parameters drawn from published sources.[82, 83] Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[84]

7 TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will sponsor the trial, although the lead organisation for contracting with NIHR is University Hospital Coventry and Warwickshire (UHCW). The day-to-day running of the trial will be managed according to Warwick SOPs.

7.2 Ethical approval

The trial will be conducted in accordance with all relevant UK regulations and guidelines.

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 prior to starting recruitment. 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 seven 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

Table 5. Trial Timetable and Milestones

Month	Time period	Activity	Milestones
Phase 1: Set up			
-4 - 0	1st Sept 2022 – 31st Dec 2022	Finalise Protocol HRA/REC submission	Submission to HRA/REC
0 - 5	1st Jan 2023 – 31st May 2023	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 - 15	1st Jun 2023 – 31st March 2024	Start recruitment (staggered start of sites). Recruit 61 participants during internal pilot (allowing 1 month from study opening to first randomisation for consent process)	16 sites open and recruiting to target 61 participants recruited

		Assess against stop-go criteria (after 9 months randomisation) Decision on trial progression	Report to DMC, TSC and HTA
Phase 3: Main trial, Analysis & Dissemination			
16-32	1st April 2024 – 31st Aug 2025	Complete trial recruitment	276 participants recruited
50	28th Feb 2027	Complete (primary) 18-month follow-up	All 18-month follow-up closed
56	31st Aug 2027	Complete 24-month follow-up	All 24-month follow-up closed
51 - 60	1st March 2027 – 31st December 2027	Data cleaning Complete Analysis Complete Analysis for primary outcome data Complete 24-month data analysis Final data review with DMC/TSC Complete monograph	Present results to DMC and TSC Final monograph, and dissemination of results

7.7 Administration

Trial co-ordination will be based at WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The TMG, consisting of 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 TSC or Investigators, as appropriate.

Smaller team meetings consisting of the Co-CIs, 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. Routine business is conducted by email, post, or teleconferencing.

The TSC, 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 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 first DMC meeting will be held jointly with the TSC (unless quorate numbers for each cannot be achieved, in which case they will be separated). Thereafter, the DMC will meet regularly as a separate committee. 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.

DMC meetings will also be attended by the Co-CI's, 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 (TMF) will be set up according to Warwick SOPs and held securely at the coordinating centre.

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

7.12 Financial support

This study is funded by the NIHR Health Technology Assessment (HTA) Programme (NIHR134398). 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 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 TMP developed and determined by the Risk Assessment undertaken prior to the start of the trial.

The TMP will be agreed by the TMG based on the trial risk assessment. Processes to be considered in the 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 Sponsor. Assessment of fidelity of the interventions will be assessed using the process and fidelity measures documented in section 3.1.1.3

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) may be considered as triggers for on-site monitoring visits. Whilst the monitors who would visit sites work in the same institution as the Co-CI's and trial team (WCTU), they will act independently of the trial team in this role. 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. Central monitoring will be performed by the trial team exploring the trial dataset or performing site visits, as defined in the TMP and data management plan.

9 PATIENT AND PUBLIC INVOLVEMENT

Patients' views have been critical in developing the trial and will continue to be important in its delivery. Two PPI representatives are co-applicants.

In the PIPS feasibility trial, we performed structured interviews with 12 participants. These have informed the study design particularly aspects of recruitment and data collection.

Prior to the funding application, we spoke to six people who have had treatment (surgery or physiotherapy) for patellar dislocation. All agreed the study was important. They were very supportive of the trial, and all would be happy to consent if they were eligible. They emphasised their uncertainty on the best management for recurrent dislocation, and its disabling effects on adolescent and adult life. They found both Personalised Knee Therapy and surgery acceptable. The importance of a comprehensive Personalised Knee Therapy package that engages patients and improves on previous treatments was a common feature. They also emphasised that function and return to work/sports were key outcomes in their views to measure a successful outcome.

In these discussions, the patients provided detailed advice as to how to communicate with potential participants considering the study, particularly what should be included in our patient information sheet and study materials, to help ensure a balanced view. They reiterated the uncertainty that they faced whilst being advised about the treatment approaches after their recurrent patellar dislocation.

We specifically asked our PPI members their views on the potential for future treatment such as surgery, if allocated to the Personalised Knee Therapy group. The group acknowledged that a change from non-surgical to surgical management may occur to people considering the trial, with three having experienced this themselves. They did not necessarily see this as a negative experience, having tried physiotherapy. One PPI member was concerned that the study could report that the non-surgical intervention was superior, after surgery had been undertaken. We have clearly accounted for this concern in our plans to perform both intention-to-treat and a secondary 'as treated' analysis. This, in her mind, re-enforced her reasoning for the importance of the trial.

The PPI group also reviewed the planned outcome packs which included the proposed primary and secondary outcome measures. They felt the length of the questionnaire booklet was “acceptable”, taking between 12 to 15 minutes to complete. They felt that people who consent to participate would be unlikely to resent this time. They felt the questions and topics being posed were important in their lives and favoured the KOOS4 over the NPI score. They felt overall function, work and sports were a more representative measure of “how they were doing” than the NPI score which was perceived as important but a different area of their lives. All six preferred a digital approach to complete and return the outcome scores but two felt that having the option of an email or paper version may be helpful for those people who may find completing electronically a “put off”. This feedback re-enforced our rationale for planning app-based data collection in addition to a paper-based option.

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 TSC. All lay representatives will be supported by the trial’s PPI Lead (DE) and Co-CI’s. Training courses for PPI members and online modules about PPI engagement have been delivered by WCTU and will be offered to all PPI members. All lay representatives will be remunerated according to INVOLVE guidelines.

10 DISSEMINATION AND PUBLICATION

The study monograph will be prepared by the TMG and other collaborators within three months of trial completion. Warwick SOPs will be followed to determine authorship. We will simultaneously prepare manuscripts (protocol paper, intervention development paper, results paper and health economic analysis paper if better reported separately) for high impact, peer-reviewed, open access journals. Summary briefing papers, press releases and social media posts (specifically aimed at UK audiences) will be prepared for the wider community with specific input from our PPI team. These outputs will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, policy makers and patients and society at large in the UK, and globally.

10.1 Patients and public

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

We will use lay summaries and infographics which will be sent to trial participants, 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 (HRA) 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. The website and associated social media channels will be used to promote study progress, increase awareness of this NIHR research, promoting social engagement across the UK and promote trial publications.

10.2 Surgical and wider community

We will register the trial with ISRCTN prior to starting and will publish the trial protocol during the recruitment phase.

Key findings will be presented at national and international conferences, such as the British Orthopaedic Association, Australian Orthopaedic Association, the American Academy of Orthopaedic Surgeons, and the Chartered Society of Physiotherapy (UK). Where this is possible, our PPI representatives will be invited to participate in the proposed conferences or meetings and with the support of the team present findings and experiences from a patient perspective.

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