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BEPKO-3

BEhaviour change for People with clinically diagnosed Knee Osteoarthritis:
A pragmatic trial (BEPKO-3)

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This protocol has regard for the HRA guidance

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CMT	Cognitive Muscular Therapy
CI	Chief Investigator
DMC	Data Monitoring Committee
DSPT	Data Security & Protection Toolkit
EDI	Equality, Diversity and Inclusion
EMG	Electromyography
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FCP	First Contact Practitioner

GAKS	Global Assessment of Knee Symptoms
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat
KL	Kellgren-Lawrence (grading for OA severity)
MMSE	Mini Mental State Examination
MSK CATS	Musculoskeletal Clinical Assessment and Triage Services
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NJR	National Joint Registry
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PCS	Pain Catastrophizing Scale
PI	Principal Investigator
PPIE	Patient and Public Involvement and Engagement
PSEQ	Pain Self-Efficacy Questionnaire
QALY	Quality-Adjusted Life Year
R&D	Research and Development
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RfPB	Research for Patient Benefit
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TSC	Trial Steering Committee

WPAI-OA	Work Productivity and Activity Impairment Questionnaire for Osteoarthritis
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

TRIAL SUMMARY

Study Title:	BEhaviour change for People with clinically diagnosed Knee Osteoarthritis: A pragmatic trial (BEPKO-3)
Short study title	BEPKO-3
Local Study Reference:	8360
Study Design:	Pragmatic multi-centre, two-arm, randomised, superiority trial with parallel groups (allocated on a 1:1 ratio) with an embedded qualitative evaluation and parallel cost-effectiveness evaluation.
Study Participants:	Adults with knee Osteoarthritis (OA) who are dissatisfied with the outcome of therapeutic exercise for their knee OA.
Planned Number of Sites:	6
Planned Sample Size:	252
Treatment Duration:	7-9 weeks
Follow Up Duration:	12 months
Intervention	Cognitive Muscular Therapy for knee osteoarthritis. A seven-week individual physiotherapy intervention which incorporates electromyography biofeedback.
Control	Usual NHS care for knee osteoarthritis
Planned Recruitment Start Date:	1st November 2025
Planned Recruitment End Date:	31st August 2027
Planned Trial End Date: (final outcomes collected)	31st June 2028
Planned Study Close Date:	30th September 2028
Research Question:	What is the clinical and cost-effectiveness of Cognitive Muscular Therapy + usual care compared with usual care alone for people with knee osteoarthritis who have received therapeutic exercise but who are dissatisfied with the outcome.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Research for Patient Benefit National Institute for Health and Care Research (NIHR) Grange House, 15 Church Street, Twickenham London, UK, TW1 3NL rfpb@nihr.ac.uk	**£** 508,138.00

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University of Salford, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this study but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The study is funded by the National Institute for Health & Care Research (NIHR). The NIHR will play no part in the running of the trial or in any data collection, interpretation or analysis of the results

Trial Management Group

The trial management group (TMG) will include of the chief investigator, trial manager, lead physiotherapist, statistician, health economist, qualitative lead, other co-investigators and at least one PPIE member. This group will meet regularly to oversee the day-to-day management of the trial and ensure it is conducted according to the protocol and will operate according to the TMG charter. Any problems with study conduct and participating centres will be raised and addressed during TMG meetings.

Trial Steering Committee

The Trial Steering Committee (TSC) will oversee and supervise the progress of the trial and ensure that it is being conducted according to the protocol and the applicable regulations. The TSC is an independent body that includes at least three external academic members (including one statistician) and at least one lay member who are not involved with the running of the trial. The chief investigator, trial manager and statistician will attend these meetings but will be there to present updates and respond to queries and will not participant in decision making. The CI and other trial team members will leave the steering committee meeting when the independent members discuss confidential issues (e.g. performance concerns). TSC Meetings will take place remotely, at least every 6 month or more frequently if required. Given the nature of this study, a separate Data Monitoring Committee (DMC) will not be convened and the TSC will also take on the data monitoring role. At the TSC/DMC meetings, the trial manager will present a summary of screening, recruitment, case report form

returns, treatment withdrawals, site monitoring, treatment adherence and adverse events. There will be no presentation of any unblinded outcome data.

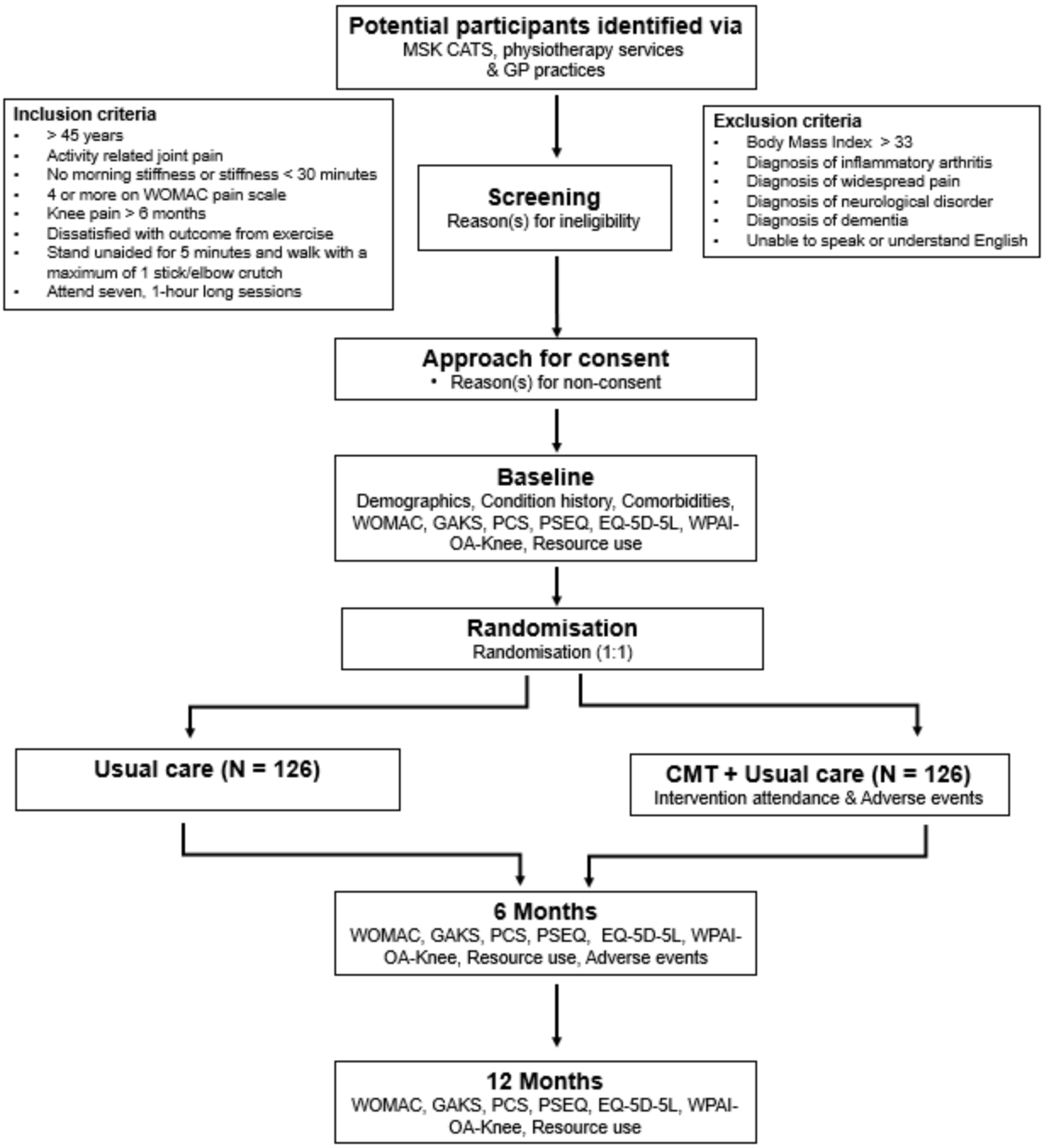
Protocol Contributors

Several protocol contributors have been involved in the development of this protocol, these include the chief investigator, lead physiotherapist, statistician, health economist, trial manager, PPI members. Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

KEY WORDS

knee osteoarthritis; physiotherapy; rehabilitation; electromyography; biofeedback; behavioural intervention

TRIAL FLOW CHART



Definitions:
MSK CATS = Musculoskeletal Assessment and Treatment Service
GP = General Practitioner
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
GAKS = Global assessment of knee symptoms
PCS = Pain Catastrophizing Scale
PSEQ = Pain Self-Efficacy Questionnaire
EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire
WPAI-OA = Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee

1 BACKGROUND

Knee osteoarthritis (OA) is a long-term condition which results in pain, disability and reduced quality of life [1]. One in three people over 40 will develop knee pain within 12 years [2] and 10% of the UK population over the age of 55 will be diagnosed with knee OA [3]. The NICE-recommended clinical pathway for people with knee OA is an initial course of therapeutic exercise [4], delivered either by a physiotherapist or exercise practitioner. If this fails, many of those affected proceed to orthopaedic referral for more invasive treatments, including total knee replacement. Over 115,000 knee replacements are carried out annually in the UK at a cost of over £500 million [5] . Such numbers, and associated healthcare costs, demonstrate that muscle strengthening does not provide sufficient symptom relief for many people with knee OA. Therefore, there is an urgent need to improve the conservative management of people with knee OA who do not respond to therapeutic exercise.

While current guidelines focus on the use of exercises to improve strength, there is clear evidence that people with knee OA over activate their muscles during functional tasks [6-8]. This overactivity is characterised by both increased amplitude [9] and prolonged duration [7] of the contraction of the knee flexor and extensor muscles. Biomechanical research has demonstrated the potentially damaging effects of these patterns, showing that muscle overaction is linked to pain [10], elevated joint load [11] and a more rapid rate of cartilage loss [12]. It is therefore important to understand the potential of conservative management techniques which focus on reducing muscle overactivity.

Psychosocial factors have been linked with clinical pain/disability in knee OA. For example, catastrophising [13] and anxiety [14] have been associated with pain intensity and kinesiophobia linked to physical function [15]. Given these links, physiotherapy interventions have been developed which integrate psychological techniques [16, 17] with muscle retraining. However, these interventions have focused primarily on muscle strength training. Therefore, it is unclear whether improved clinical outcomes would be obtained if psychological techniques were integrated with training to reduce muscle overactivity.

2 RATIONALE

Through two research projects (funded by the NIHR) awards we have created, and feasibility tested, a new physiotherapist-led intervention for knee OA [18], called 'Cognitive Muscular Therapy (CMT)'. CMT is an integrated behavioural intervention which integrates psychological techniques for pain management with biofeedback training to reduce muscle overactivity. CMT is delivered through five sequential components, which guide people through a learning journey. As they progress through the treatment, existing illness beliefs are challenged, individuals form a new conceptual model for their condition and learn to change habitual responses to pain. They also learn to consciously reduce overactivity of the knee muscles in standing and during functional tasks.

Our feasibility data demonstrate that the CMT intervention is acceptable to both people with knee OA and physiotherapists and suggest it may deliver medium/large improvements in pain in comparison to usual care. However, in comparison to exercise, which can be delivered in a group setting, the CMT intervention is more resource intensive, requiring seven individual physiotherapist sessions. We therefore propose that CMT should be offered on the NHS if patients with knee OA have tried, but are dissatisfied with, therapeutic exercise. By positioning CMT as second-line treatment, after exercise but before costly orthopaedic referral, we anticipate

more appetite for CMT to be adopted into NHS care pathways. This study has therefore been designed to compare CMT + usual care with usual care alone for people with knee OA who have received therapeutic exercise but who are dissatisfied with the outcome.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Aims

The primary aim is to assess whether Cognitive Muscular Therapy (CMT) + usual care results in less knee pain and disability at 1-year post-randomisation compared to usual care alone. We hypothesise that CMT + usual care will be associated with lower composite WOMAC scores at 1 year in comparison to usual care alone for people with a clinical diagnosis of knee OA (OA), who are dissatisfied with the outcome of therapeutic exercise.

Secondary aims include:

- Estimates of treatment effects across a range of secondary outcomes including knee pain, knee function, knee stiffness, pain catastrophizing, pain self-efficacy, global assessment of knee symptoms, quality of life, the impact of knee OA on capacity to work, healthcare use (including knee replacement surgery) and adverse events up to 12-months.
- Within-trial cost utility analysis from an NHS and PSS perspective.
- Qualitative exploration of participants and physiotherapists' experiences and perception of the CMT intervention, beliefs around implementation and involvement in the trial.

3.2 Primary Outcome

The primary outcome will be the WOMAC (Western Ontario and McMaster Universities OA Index) composite score [19] at 12 months from randomisation. WOMAC v 3.1 will be used which is composed of three subscales: pain (5 questions), physical function (17 questions) and stiffness (2 questions). Each item is rated on a scale of 0 to 4 (with higher scores indicating worse pain, function, and stiffness), giving a total score ranging from 0 to 96 capturing pain/functional limitation/stiffness from both knees. This outcome is routinely used in large-scale clinical trials of knee OA [20-23] and will therefore facilitate comparison with other clinical trials in this population.

3.3 Secondary Outcome measures and endpoints

- Composite WOMAC score [19] at 6-months post-randomisation
- WOMAC pain subscale [19] at 6- and 12-months post-randomisation
- WOMAC function subscale [19] at 6- and 12-months post-randomisation
- WOMAC stiffness subscale [19] at 6- and 12-months post-randomisation
- Global assessment of knee symptoms (GAKS) at 6- and 12-months post-randomisation [24]

- Pain catastrophizing scale (PCS) [25] at 6- and 12-months post-randomisation
- Pain self-efficacy questionnaire (PSEQ) [26] at 6- and 12-months post-randomisation
- Impact of knee OA on capacity to work will be measured with the Work Productivity and Activity Impairment Questionnaire (WPAI-OA) [27] at 6- and 12-months post-randomisation.
- Health-related quality of life will be measured using the EQ-5D-5L at 6- and 12-months post-randomisation. The EQ-5D-5L [28] is a validated measure of health-related quality of life in terms of 5 dimensions (mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, anxiety and depression) each with 5 levels of severity.
- Healthcare resource use at 6- and 12-months will be measured via a custom questionnaire, based on the Client Services Receipt Inventory. Included within this questionnaire will be additional physiotherapy (above that provided to the CMT arm), GP appointments, corticosteroid injections, surgery, imaging, hospital stays and medication use.
- All-cause mortality.
- Adverse events attributable to the trial.
- Serious adverse events.

Our choice of outcomes includes instruments to capture pain, stiffness, activity limitation, psychological factors, global assessment of knee symptoms, quality of life, healthcare resource utilisation and adverse events, including mortality. This outcome set is sufficiently broad to include all components of a core outcome set recommended by OMERACT-OARSI (Outcome Measures in Rheumatology-Osteoarthritis Research Society International) for clinical trials in knee osteoarthritis [24].

4 TRIAL DESIGN

Pragmatic multi-centre two-arm randomised, superiority trial with parallel groups (allocated on a 1:1 ratio) with an embedded qualitative evaluation and cost-effectiveness evaluation.

5 TRIAL SETTING

This is a multi-centre randomised controlled trial, taking place in physiotherapy services based in NHS hospitals across the UK. We expect to open six sites, with scope of increasing this number if required. To ensure inclusivity we will work with a range of NHS hospitals serving diverse communities in rural and urban communities. At each site there will be two physiotherapists who will be trained to deliver the CMT intervention. Participants in the CMT arm of the trial will receive the CMT intervention at one of these research sites.

All sites are expected to be recruiting sites, undertaking all research activities. At each site, the CMT intervention will be delivered within a dedicated physiotherapy clinical space. However, in the case that a particular trust is unable to provide space for intervention delivery, a GP practice or community space (such as a private room in a community centre) within close proximity of the research site, will be used to deliver the

CMT intervention. The intervention may also be delivered within a dedicated clinical space at the University of Salford which is close to one of the research sites.

6 TRIAL TREATMENTS

6.1 Details of the control intervention

For patients who have not benefited from NICE-recommended therapeutic exercise, usual care includes treatments such as pharmacological management, intra-articular steroid, and surgery [4]. Participants in the control arm will be instructed to access this care as they would if they were not involved in the trial.

6.2 Details of the Cognitive Muscular Therapy (CMT) intervention

Participants in the CMT arm will be instructed to access care as they would if they were not involved in the trial and will also receive the CMT intervention. This section provides a complete description of the CMT intervention, covering each of the items proposed in the TIDierR (Template for Intervention Description and Replication) framework [29]. The CMT intervention was developed at the University of Salford between 2018-2023 [18] through an iterative co-design process. The aim of CMT is to improve coordination of the knee muscles, reduce mechanical loading on the knee and change psychological responses to pain. CMT specifically targets overactivity of the knee muscles because this patterns has been linked to increased compressive loads on the joint surface [11], accelerated disease progression (cartilage loss) [12], increased likelihood of knee replacement at 5-year follow up [30] and increased pain [31, 32]. The CMT intervention is delivered by a physiotherapist across seven individual clinical sessions, each lasting approximately 1 hour. Intervention sessions are typically delivered weekly, but this depends on participant availability and gaps of 2-3 weeks between some intervention sessions are acceptable.

Equipment required to deliver the intervention:

The intervention requires a clinical space with an adjustable height plinth and chair. In the latter stages of the intervention, access to a staircase is required (to practice stair ascent/descent) along with a space to practice walking. The clinical space needs to be equipped with a desk, computer and electromyography (EMG) system. The EMG system is used to provide biofeedback, providing a visual representation of the level of activity in the quadriceps muscles during specific activities (stages of the protocol). For this study, we will use the Biometrics (Newport, UK) wireless EMG system within its intended statement of use. This system is CE marked and meets EU/UK Medical Device Regulation (207/745). We have selected this EMG system because of its low cost, ease of clinical use and reliability (tested in previous studies run by the University).

The CMT intervention comprises five components: Understanding knee pain, General relaxation, Postural deconstruction, Contextual triggers and Functional integration.

Component 1 (Understanding knee pain):

The aim of the first component is to challenge inappropriate illness beliefs and to enable the participant to reconceptualise the mechanisms which are likely to underlie knee OA pain. During this component the

participant watches three videos. After each video, there is a discussion with the physiotherapist to challenge inappropriate beliefs and to ensure that concepts have been fully understood. The first video is designed to challenge beliefs which are inconsistent with the therapeutic focus of CMT. Key beliefs relate to the idea that activities which exacerbate pain should be avoided, that knee pain is always the result of structural damage and that continued muscle strengthening is required to maintain knee function once knee OA has been diagnosed. The second video explains how increased activity of knee muscles can negatively affect anatomical structures around the knee. The final video explains how psychological factors, such as pain-related fear and pain catastrophizing are likely to shape the pain experience, integrating principles from therapeutic neuroscience education. In the second and third videos, participants are taught about the need to become aware of habitual responses to pain and to become aware of how pain can trigger muscle tension and/or pain-related fear which can then further exacerbate knee pain.

Component 2 (General relaxation):

The aim of the second component is to raise awareness of elevated low-level activity in the quadriceps muscles and in the muscles of the torso, hips and shoulders. Participants begin by learning diaphragmatic breathing in supine to gain a sense of elevated muscle activity in the abdominal wall. Passive limb motions in supine are then used to raise awareness of increased muscle activity around the hips and shoulders. EMG biofeedback (electrodes placed on vastus lateralis) is then used to guide relaxation of the quadriceps muscles, first in lying, then sitting and then during supported standing (leaning against the plinth). In each position, the physiotherapist guides the participant to relax the quadriceps through manipulation of the patella. Through this process, participants gain experiential learning of what it feels like to relax the anterior knee muscles.

Component 3 (Postural deconstruction):

The third component of the intervention focuses specifically on improving the organisation of postural tone (low-level muscle activity which supports the body against gravity). This focus on postural tone is critical as increased flexor tone can drive compensatory activation of the extensor muscles, including activation of the quadriceps muscles, which will increase mechanical loading on the knee [18]. To understand this concept, participants watch an animated video which depicts a ‘tug-of-war’ between flexor and extensor muscles. They are then taught to recognise patterns of compensatory extensor tone in spine, hips and knees while transitioning from a flexed to an upright position. Guided by the physiotherapist, they learn to identify a ‘tension point’ where extensor compensation becomes apparent and where the quadriceps muscles activate (visualized using EMG). Working in a flexed position allows participants to appreciate the links between flexor tone, extensor compensation and unwanted activation of the knee muscles. Through hands-on guidance, participants learn to increase costovertebral motion, increase range of trunk rotation, and to lengthen abdominal and neck muscles, thereby reducing flexor tone. At the end of this component, the aim is for participants to stand upright without compensatory extensor tone and with relaxed quadriceps muscles.

Component 4 (Contextual triggers):

In the fourth component participants learn that anticipating pain-provoking tasks can become associated with increased flexor tone and inappropriate contraction of the quadriceps muscles. They also learn that common daily activities, such as working at a computer, may trigger elevated flexor tone. To address these ‘conditioned’ responses participants are guided to mentally rehearse specific situations without triggering undesired increases in abdominal tone (monitored through visual inspection of abdominal wall excursion) or quadriceps activity (monitored via EMG). In the final stages of this component participants learn to initiate potentially pain provoking activities, such as stair ascent/descent without inappropriate activation of the quadriceps muscles.

Component 5 (Functional integration):

The final component focuses on integrating the learning from the previous four components. The goal is to enable participants to perform a full range of functional activities with minimal pain. Participants select activities from a comprehensive set that covers the full range of tasks assessed by the WOMAC questionnaire score [19]. This includes standing, walking, stair ascent/descent, bending, dressing etc. Guided by the physiotherapist, the participants practice performing each task with an optimal pattern of postural tone and without inappropriate activation of the quadriceps muscles.

Intervention delivery, home practice & self-management:

During the seven hour-long sessions, the physiotherapist works through a clearly delineated protocol which follows the intervention structure described above. Each stage of the protocol allows for tailoring to individual participant needs, e.g. psychological factors/different learning styles. Between each clinical session, participants are given 3-4 specific 'challenges' which require them to improve awareness of muscle tone, improve their capacity to relax the quadriceps muscles and change their psychological responses to pain. After each session, the participant is provided with a summary sheet which lists learning points and summarizes each challenge. To facilitate this learning/practice, participants are provided with access to an online platform which includes both written documents and animated videos. If participants are unable to engage with the online platform (e.g. no access to the internet), they are provided with a paper booklet. Following completion of the treatment, the aim is that the new muscle coordination patterns become habit. Therefore, while participants are encouraged to continue to practice the different challenges, the primary aim is that they have skills and knowledge to self-manage their knee OA, including any pain flare ups, as they go about their daily life.

Risk assessment:

This CMT intervention is very low risk. To date, we have delivered implementations of the CMT intervention to over 200 participants with no adverse events. Nevertheless, we have created a risk assessment (see 'CMT for musculoskeletal conditions - risk assessment') which will be used as part of the training that the CMT physiotherapists receive (see sections below). This includes standard precautions in rehabilitation, such as minimising infection risk, checking equipment regularly and ensuring there are no hazards which could cause a trip or fall. In addition, the physiotherapist will monitor for any allergic skin reaction to the EMG sensors and monitor for any dizziness which may result from inappropriate practice of the CMT breathing exercises.

6.3 Identification of physiotherapists who will deliver the CMT intervention

We will identify two physiotherapists who will deliver the CMT intervention at each of the research sites. We aim to set up a minimum of six research sites (12 physiotherapists) but may look to increase the number of sites if recruitment is lower than anticipated. These physiotherapists will be identified through NHS departments. To be included in the trial, we will ensure that all physiotherapists meet the following criteria:

1. Have at least 3 years' experience of treating patients with chronic musculoskeletal pain on the NHS.
2. Currently employed in the NHS to treat patients with chronic musculoskeletal pain.
3. Be willing to undertake the CMT training (detailed below), including online and face-to-face training.
4. Be available for at least 3 hours per week for a period of 1 year to deliver the CMT intervention.
5. Not involved in delivery of care to control participants

6.4 Physiotherapist training to deliver the CMT intervention

Training and assessment of the 12 physiotherapists will follow a two-stage process. The first stage in an online course, comprising of 15 separate modules, each taking 30-90 minutes to complete. These modules cover underpinning research in knee OA, background theory to CMT, principles of psychologically informed physiotherapy and the use of EMG biofeedback. The latter modules focus specifically on the specific protocols which are used to deliver the CMT intervention. During the online modules, animated videos are used to convey intervention theory and treatment footage used to explain the hands-on techniques used to guide muscle re-education.

Once the online course is completed, physiotherapists attend three face-to-face workshops, each lasting one day. At these workshops, the physiotherapists gain confidence at using CMT intervention techniques, following the CMT protocols and in using EMG biofeedback. During the workshops the physiotherapists develop their skills by practicing on both medical actors and real patients with knee OA. While the first day is more introductory, by the end of the second day physiotherapists complete a competency assessment to certify that they have sufficient knowledge to deliver CMT to patients with knee OA.

To identify patients who will attend the face-to-face workshops, we will recruit via non-NHS mechanisms (social media, poster, university database) following the procedures described in Section 8.1. This will include the use of a separate web page (https://hub.salford.ac.uk/volunteer-for-research/studies/bepko3-training/) to provide participant information and collect screening data. Note that the same web screening form as described later (see 'Web screening form') will be used to collect these data. Following our standard procedures, participants will be provided with the training information sheet (see 'Participant information sheet (Physiotherapist training)') and given at least 24 hours to read and understand the information. They will then be consented by a member of the research team using the training consent form (see 'Consent form (Physiotherapist training)'). This consenting will follow the same process as described in Section 8.3.

Consenting participants will receive the CMT treatment from the research team before/after the training day and may receive some treatment during the training day. They will also be asked if they would be happy to be recorded during treatment (this recording is optional) and for this footage to be used for future online training of health professionals. If participants do consent to being recorded, the video recording will be stored in a secure server managed by the University of Salford, all identifying features will be removed and then they will sign a video release from (see 'Video release form'). If videos are retained for future training, participants will receive a payment of £100. If videos are not used, they will be permanently deleted. We will not collect outcomes from participants who are consented for physiotherapist training but will retain contact details for the duration of the trial so that they can be sent a summary of the study findings.

To provide the physiotherapists with the opportunity to practice delivering CMT after the second face-to-face workshop, we will provide them with the option of consenting patients to receive the CMT treatment using the training participant information sheet (see 'Participant information sheet (Physiotherapist training)' and 'Consent form (Physiotherapist training)'). These patients will be identified by the physiotherapist as an individual who is currently under their care for knee OA and who is happy to receive the CMT treatment. We will ensure that any physiotherapist who consents has completed mandatory GCP training and that the screening and consenting processes described in the protocol are followed. The consent form and contact details of the participant will be stored by the research team. Again, we will not collect outcome data from participants consented for physiotherapist training, however, we will retain contact details for the duration of

the trial so that they can be sent a summary of the study findings. To accommodate different learning styles, we recognise that some physiotherapists may not feel it necessary to practice independently on patients and will be happy to continue to practice working through the CMT protocols with professional colleagues.

After a period of 1-3 months (depending on physiotherapist preference and timing of recruitment for the main clinical trial), physiotherapists will be invited back for a third (final) face-to-face workshop. At this workshop, the research team will go through any aspects of the CMT protocols which the physiotherapists have found particularly challenging to understand/deliver and then carry out a final competency check. For this final check, physiotherapists will be expected to have in-depth knowledge of the protocols and have memorised every stage.

Experience from previous trials shows that physiotherapists require exposure to a range of different presentations of knee OA before they can be fully confident in adapting and applying the CMT protocols for different patients. Therefore, we propose to provide direct supervision for each physiotherapist when they treat the first 3-4 participants. This supervision will be provided by a member of the research team either through direct observation or through video recording and subsequent follow-up. We recognised that some participants may not feel comfortable with being videoed and therefore we will make this optional. All recordings will be stored securely on a University of Salford server and deleted once analysis has been completed, typically within 2-3 weeks of the recording.

6.5 Treatment log

The physiotherapist will record the date and length of each of each treatment sessions for every participant in the CMT arm. These data will be transferred from the treatment log to the secure trial database by the trial manager (or another member of the team who is not blinded to group allocation) to provide a measure of attendance (date of first intervention session, date of final intervention session and total number of sessions attended). In addition, the following data will be recorded during the CMT treatment by the treating physiotherapist:

Table 1: Treatment log

	Time point	Description	Collected by
Clinical notes	After each clinical session	A pro forma will be used to summarise clinical presentation and capacity to engage with intervention techniques	Physiotherapist
Participant engagement score	At start of clinical sessions 2-7	The physiotherapist will assess: 1. Engagement with the online learning platform 2. Written reflections on home practice (patient summary sheet) 3. Competence and understanding of previous week's challenges (home practice) Based on this assessment, the physiotherapist will determine a weekly engagement score: 1. 0 = not engaged 2. 1 = low engagement	physiotherapist

		3. 2 = full engagement	

The weekly engagement score will be recorded in the clinical notes but will not be used as part of any analysis of trial outcomes. If scores are consistently below 2 then the physiotherapist will spend time at the end of each clinical session discussing barriers to engagement and creating an action plan with the participant to improve engagement and home practice.

6.6 Assessment of intervention fidelity

Intervention fidelity will be assessed for each physiotherapist who delivers the CMT intervention. This assessment will be carried out after they have completed treatment on the first 3-4 participants under supervision of a member of the research team (see above). For each physiotherapist, we will video record at least two intervention clinical sessions for each of the seven clinical CMT sessions (14 recordings per physiotherapist). Using a 25-point checklist, a member of the research team will score physiotherapist's ability to deliver each stage of the CMT protocols. After scoring the full set of 14 recordings, the final score will be converted to a percentage.

6.7 Potential for contamination

CMT is not currently available on the NHS and is only delivered through research studies which are being run by the University of Salford. Therefore, at present, it is not possible for patients outside this trial to access this treatment. However, this situation may change during the trial as we may offer training in CMT to private physiotherapists. In this situation, participants in the control arm could potentially access CMT through private providers, resulting in contamination. To mitigate against this, we have omitted the name of the CMT intervention from the participant information sheet. We will also collect information on physiotherapy accessed during the trial through the healthcare resource questionnaire (see 'Healthcare resource use questions').

6.8 Criteria for discontinuation of interventions

The CMT intervention is low risk and therefore we do not anticipate the need to discontinue this treatment because of any harm to participants or worsening of any disease. However, if participants request to discontinue treatment, they will be provided with the option of staying in the trial and returning outcomes or of complete withdrawal from the study.

7 PARTICIPANT ELIGIBILITY CRITERIA

The CMT intervention has been positioned as a second-line intervention for people with knee OA which would be offered to NHS patients if they have tried therapeutic exercise and are dissatisfied with the outcome. We will therefore recruit patients with a clinical diagnosis (according to NICE) of knee OA [4] and who have

received NICE-recommended therapeutic exercise but who are dissatisfied with the outcome. The following inclusion/exclusion criteria will be used:

7.1 Inclusion criteria

- Over 45 years of age
- Activity-related knee joint pain
- No morning stiffness or morning stiffness that lasts less than 30 minutes
- Score 4 or more (out of 20) on the WOMAC pain scale [19]
- Experienced knee pain for longer than 6 months
- Tried a structured programme of therapeutic exercise and be dissatisfied with the outcome (assessed via screening question). As a minimum, participants must have either seen a healthcare professional and been provided with a structed exercise programme or given access to an NHS exercise App (e.g. getUBetter). The programme could have been undertaken independently or supervised (e.g. an exercise class).
- Able to stand for 5 minutes unaided and walk independently with a maximum of one walking stick/elbow crutch (required to complete the intervention).
- Able to attend for seven hour-long intervention sessions with a physiotherapist

7.2 Exclusion criteria

- BMI>33 (as increased subcutaneous fat prevents collection of EMG signals)
- Inflammatory arthritis including rheumatoid arthritis, psoriatic arthritis, ankylosing arthritis, enteropathic arthritis, lupus, septic arthritis or gout.
- Diagnosis of a widespread pain condition, such as fibromyalgia
- Neurological disorder, such as multiple Sclerosis, cerebral palsy or previous stroke (with ongoing neurological deficit)
- Diagnosis of dementia and score >17 on the Telephone-Mini mental state examination (T-MMSE) for cognitive impairment [33]. Note that the T-MSSE (see 'Telephone_MMSE') will only be collected (via telephone) from participants who have a confirmed medical diagnosis of dementia.
- Unable to speak and understand English sufficiently well enough to receive the intervention

8 TRIAL PROCEDURES

8.1 Participant identification and screening

We propose identifying potential participants via five mechanisms:

1. Through NHS musculoskeletal physiotherapy departments
2. Through NHS musculoskeletal assessment and triage/treatment services (MSK CATS)
3. Through GP practices and First Contact Practitioners (FCPs)
4. Via Social media advert, the University of Salford Hub advert and posters

5. Through a database of volunteers held at the University of Salford

1 NHS physiotherapy departments – research site

NHS physiotherapy departments will be set up as research sites with local staff undertaking screening and consenting activity. In situations where local staff have limited capacity for recruiting and consenting, then research staff (at the University of Salford) will screen and consent participants. However, research staff at the University will not have direct access to patient information and will carry out full screening only after the participant has independently contacted the University or has provided consent to contact. With this approach, initial searching of NHS patient records/patient identification will always be undertaken by the patient's direct care team with full screening undertaken by either local site staff or University of Salford staff.

Potential participants in physiotherapy departments will be identified through searching of electronic records or during routine clinical consultation. This consultation will include individual treatment sessions, during group exercise classes or at the at the point of discharge from NHS clinical services. Electronic searching will be carried out by direct healthcare team members to identify people with a relevant diagnostic (SNOMED CT) code for knee OA. The resulting patient lists will then be screened to rule out patients who do not meet eligibility criteria. Eligible participants will then be sent an invitation letter (see 'Letter of invitation') and participant information sheet (see 'Participant information sheet (Clinical trial)') and asked to contact the local team. The local team may choose to follow-up the initial invitations with a phone call or send a reminder. Participants who contact the local team will undergo full screening following local procedures.

If local staff do not have the capacity to undertake full screening and consent, then participants will be instructed to contact the University research team. In this situation, participants identified after the initial search will be sent either the participant information sheet (and letter of invitation) or send a text message invitation to participate (see 'Text Invitation'). The text message contains a link to a webpage which provides an overview of the study. Similarly, the participant information sheet also contains the link along with QR code for this web page. Note that this page (https://hub.salford.ac.uk/volunteer-for-research/studies/bepko-3-trial/) which will ultimately contain a link to the participant information sheet. Embedded within the webpage will be a link to an online form which volunteers will complete if they are interested in taking part. The questions from this form have been copied to the document 'Web screening form'. All data submitted via these forms is strictly confidential and held on a secure server at the University of Salford. If participants do not want to complete an online form, they are still free to contact the research team directly if they would prefer to be screened over the phone. With either of these two approaches, the research team will not have access to patient records. However, in some cases, patients may learn about the study from NHS staff (direct care team) and may be happy for their contact details to be passed directly to the research team at the University of Salford. In this situation, participants will complete a consent to contact form (see 'Consent to contact form'). A contact email/phone number will then be passed to the research team via secure NHS email. This will allow the research team to contact the participant directly to undertake a full screening.

2 Musculoskeletal triage services (MSK CATS) – Participant identification centre

NHS patients with knee OA are typically referred to MSK CATS service from their GP once they have tried, but are dissatisfied with the outcome of therapeutic exercise. This triage service is the gateway for onward referral onto orthopaedic management of chronic knee pain. We will use these services as participant identification centres, identifying MSK CATS service within close proximity of each research delivery sites. We will use the

same approach for participant identification and screening as described for NHS physiotherapy services, either at the point of clinical consultation or by screening electronic records and sending text message invitations or letters of invitation. If the local team does not have capacity to screen and consent, then the research team will undertake these activities. The research team will not have access to patient records but will receive details of the number of invitations sent by each MSK CATs team.

3 GP practices – Participant identification centre

We will identify GP practices within close proximity of each of the research delivery sites to act as participant identification centres. We will follow the same procedure as outlined above, identifying participants through electronic searching patient records diagnostic (SNOMED CT) code for consultation for knee OA within the last 48 months. Following screening of the list of people identified through the search (by a member of the direct care team), invitations will be sent via letter or text message. Full screening and consenting will be undertaken by research staff at the University of Salford once participants independently make contact with the research team. We note that the research team will not have access to patient records but will receive details of the number of invitations sent by each GP.

4 Social media advert, University of Salford Hub advert and poster

We will use social medial channels, such as Twitter (X), Facebook, and Instagram to promote the study (see 'Social media advert'). We will use also use the University of staff internal hub (web page) to promote the study (see 'Hub advert'). Individuals who are interested in participating in our research will be directed to the webpage described above. We will also place poster advertisements (see 'Poster') around the University of Salford and within NHS sites, such as GP practices or physiotherapy departments. We will also put the poster in community sites, such as churches/mosques and shopping centres. The poster contains a QR code, which links to the webpage described above. We will ensure that we have appropriate permissions before placing posters in community settings, e.g. from church officials. With this approach, full screening and consenting will be undertaken by research staff at the University of Salford.

5 University of Salford database – Participant identification centre

At the University of Salford, we hold a database of people interested in knee OA research. People registered on these databases who live within 30 minutes travel of one of the research sites will be sent the participant information sheet and the invitation letter or sent a text/link to the webpage, described above. With this approach, full screening and consenting will be undertaken by research staff at the University of Salford.

Strategy to ensure representation across different social/demographic groups

We will assess the diversity of ethnicity and socioeconomic status across each GP practice, physiotherapy and MSK CATS service. This information will then be used to guide choice of recruitment sites to maximise the likelihood that participants from underrepresented groups will volunteer to participate. As part of our baseline dataset, we will collect data on EDI characteristics, such as ethnicity, sexual orientation and religious beliefs (see 'Diversity and inclusion survey'). We highlight that provision of these data are optional and participants who are not willing to provide this information will still be included in the study. Ethnicity and socioeconomic data will be reviewed regularly by the TMG and TSC to ensure that the sample of participants recruited is representative of the target population. If we identify any issues with the diversity of our sample, we will

engage in community recruitment (posters and social media), specifically targeting places where we can identify underserved populations, such as community centres or places of worship.

Screening of participants

With the methods of recruitment described above, participants will either contact the local team or the research team (at the University of Salford) once they have read the participant information sheet and are interested in participating. If the local team have capacity, they will perform a full screening using the full inclusion/exclusion criteria stated set out in the previous section. The local team will then confirm eligibility.

Participants may contact the University research team either via phone call or email or by completing the online screening form. Participants who are deemed ineligible through the screening form will receive a text message or email (depending on preference) to explain that they are unable to take part. Those who appear potentially eligible (after completing the form) or who contact the team directly, will undergo telephone screening to confirm that all inclusion/exclusion criteria are met. With this approach, the research team will confirm eligibility and record name, contact details and NHS number (if available) for those who are eligible.

Screening data will be collected from each participant and will capture:

1. Number of participants screened
2. Numbers of participants eligible
3. Reasons for ineligibility (if applicable)
4. Numbers of participants consented
5. Reasons for decline (if applicable)

Any information from participants who do not fulfil the study's criteria (including data collected through the online form) will be permanently deleted and only the data listed above will be recorded. However, before deletion, participants will be send an email invitation, with a link, to join a database of volunteers for future knee OA studies (see https://hub.salford.ac.uk/volunteer-for-research/volunteer-databases/knee-pain-database/). This is completely voluntary, and no data collected during screening will be transferred to this database.

8.2 Payment

All participants, irrespective of group allocation, will receive £20 at the point when the invitations to complete outcomes (both at 6-months and 12-month outcomes) are sent. These payments will not be conditional on completion of outcomes and will be made via bank transfer.

8.3 Consent

All participants will have the opportunity to read the participant information sheet before they reach out to the local team or research team. Full screening will be undertaken via telephone call by the research team and may be undertaken by phone or face-to-face by the local team. Once deemed eligible, participants will have the

opportunity to ask for clarification on any aspects of study participation, trial processes or any issues related to personal circumstances. The recruiter will then read through the consent form with the participant and ensure understanding. The participant will either initial the boxes and sign the consent form (if face-to-face) or be sent a copy of the consent form in the post (see 'Consent form cover letter') and asked to initial all the boxes and sign (if telephone). They will also be asked to complete the data access form (see section on Baseline data below) at the point of consent. The GCP trained staff member who carries out the consenting process countersigns the consent form indicating all available information has been given to the participant. The consent form and data access forms are then returned to the University/local site either via a scan/photo or via pre-paid postage envelope.

It will be the responsibility of the local site Principal Investigator (PI) to ensure that all staff who take consent are appropriately trained and on the delegation log for the study. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study.

Reasons for declining participation, where given, will be recorded on the screening log.

For participants who are eligible, the research team or local team will record the following details:

1. Name
2. Date of birth
3. Contact telephone number
4. Email address
5. Home address
6. GP practice
7. NHS number (if known)
8. Any preference for physiotherapy appointment times.

Once the consent form (see 'Consent form (Clinical trial)') and data access (see 'Data Access Form') form have been received, the participant will be formally enrolled onto the study. With the participants' permission, the research team will then send a letter to the GP (see 'Letter to GP') informing the GP of the participants' participation in the study. If participants do not return the consent from within the specified period (see Section 7.8), all personal data (listed above) will be deleted.

Physiotherapists consent for focus groups

We will obtain consent from the physiotherapists who deliver the CMT intervention (as part of this trial) to attend an online focus group (see 'Participant information sheet (Physiotherapist focus group)' and 'Consent form (Physiotherapist focus group)'). If they do not consent to attend the focus group, physiotherapists will still be able to work on the trial to deliver the intervention. Full details of the qualitative component to the study is provided in Section 8.8.

8.4 The randomisation scheme

Once the consent form is returned, then participants will be registered on the secure trial database. This database will be created by Northern Care Alliance (NCA) using the REDCap platform and used to store all clinical data for the study. The trial database will allow collection of electronic outcomes and will be fully auditable. Full details are provided in Section 11.1.

Once participants return baseline data (Section 8.6) and baseline outcomes (Section 8.7), they will be randomised in a 1:1 allocation ratio to either the CMT + usual care arm or the usual care arm. In summary, restricted randomisation will be employed, using stratified block randomisation with variable block sizes. Stratification will be by site to ensure balance in the number of participants allocated to each treatment arm within sites, minimising practical challenges with physiotherapy timetabling and intervention delivery. The use of variable block sizes will maintain allocation concealment and reduce the risk of prediction of future allocations.

The randomisation sequence will be generated in advance by the trial statistician using the *ralloc* command in Stata (StataCorp, College Station, TX, USA), which provides an algorithm for stratified block randomisation with variable block sizes. To preserve allocation concealment, the sequence will be held securely within a password-protected document maintained by the trial statistician. Details of block sizes and the randomisation seed will be stored in a restricted-access document available only to the statistician and the data management team and will not be accessible to other investigators or site staff.

Each participant's allocation will be logged within the secure trial database, creating an auditable record which will only be accessible to the trial manager and trial statistician.

8.5 Blinding

This is a pragmatic trial which aims to compare an active physiotherapy treatment with a care-as-usual group. As such, blinding of participants to group allocation is not feasible. However, we propose several steps to ensure blinding of outcomes assessors and to minimise bias from knowledge about group allocation. Firstly, where participants are happy to complete electronic outcomes, all data will be collected using the secure trial database. This database will automatically send participants an individual link to complete outcome data and these links will not be accessible to the study team. Monitoring of the return of outcomes will be performed by a member of the study team who is blinded to group allocation. When participants fail to respond to reminders to complete electronic outcomes, they will receive a call from a member of the research team to complete a minimum dataset (see Section 8.8 for more details of the reminder schedule). This team member will also be blinded to group allocation and will add all information directly into the secure trial database. This data will be date-stamped and linked to the corresponding team member for subsequent auditing. Some participants may prefer to complete outcome data via postal questionnaire. These data will also be entered into the trial database document by a member of the team who is blinded to group allocation, with metadata to enable subsequent auditing.

8.6 Baseline data

To characterise the sample of participants, we will collect data using a baseline and diversity inclusivity survey (see 'Baseline data and diversity inclusivity survey') which will be completed at the same time as the baseline outcomes. It will capture:

1. Gender
2. Age

3. Weight
4. Height
5. Knee{s) affected
6. Duration of knee pain symptoms in at least one knee
7. Co-morbidities
8. Religion
9. Socio-economic status
10. Ethnicity

Data on diversity and inclusivity have been requested by the funder and will allow us to demonstrate that we have a representative sample when we publish the study findings. Data on ethnicity and socio-economic status will be reviewed at each TSC meeting to monitor the representativeness of the sample as the trial progresses.

In addition to sociodemographic characteristics and pain duration, we propose to characterise the radiographically measured severity of OA using the Kellgren-Lawerence grade score 0-4, (0= normal, 4 = severe OA). However, we do not propose collecting x-ray data. Instead, we will request access to participant's previous x-rays via the data access from (see 'Data access from') which will be sent out with the consent form (as explained above). Once we have access permission, the research team will work with radiography departments to obtain Kellgren-Lawrence for participants who have had a previous x-ray. Based on only our previous feasibility study, we anticipate being able to obtain these data for approximately 50% of participants.

8.7 Trial assessments and follow-up

The schedule of assessment is summarised in the table below. Following screening, eligible participants will return the consent form with the data access form (which provides permission to access x-ray data). Once received, the participant will then be asked to complete the Baseline data and diversity inclusivity survey, WOMAC [19], Pain catastrophizing scale (PCS) [25], Pain self-efficacy questionnaire (PSEQ) [26], Work Productivity and Activity Impairment Questionnaire (WPAI-OA) [27], EQ-5D-5L [28], healthcare resource utilisation along with the baseline qualitative survey (see 'Baseline qualitative survey'). As explained above, these data will be collected using the secure trial database. If participants prefer to provide data via a written document, they will be sent paper copies of every questionnaire in the post and provided with a stamped addressed envelope to return completed questionnaires.

Once baseline questionnaire data have been received, participants will be randomised. The timing of the two subsequent outcome data collection points will then be set based on the date of randomisation. We will aim for participants allocated to the CMT arm to begin treatment within 7 weeks of randomisation and for the intervention to be delivered over a 7-9 week timeframe. With this timeframe, all intervention sessions would be completed by four months (from the data of randomisation). However, we will allow some flexibility ensuring an upper limit of six months (from the data of randomisation) for completion of all intervention sessions. This will ensure that intervention is complete by the first follow-up outcome point. Follow-up data will be collected at 6 months and 12 months (from the date of randomisation), using the trial database or postal questionnaires (depending on participant preference). At 6 months and 12 months we will collect data using the same outcomes as baseline with the addition of the Global assessment of knee symptoms (GAKS) [24], which asks patients to recall change from

baseline (see Table 2 below). All data collected via postal questionnaire or minimum dataset will be entered into the trial database by a member of the research team who is blinded to group allocation.

Following randomisation, the intervention coordinator (member of the research team) will liaise with participants in the intervention arm to schedule the intervention sessions. Once scheduled, participants will be sent a participant appointment information letter and schedule (see 'Group 1 Participant appointment letter'). Participants in the control arm will be sent the group 2 allocation letter (see 'Group 2 Allocation letter'). In some cases, research sites may use their own processes for booking and scheduling appointment. In this scenario, participants in the control arm will still be send the same letter, however, participants in the CMT arm may receive the same information from their trust in a different format.

During the CMT treatment, the treating physiotherapists will keep a log of the number and length of appointments attended and will also record a weekly engagement score, as described in Section 6.5. Only attendance data will be used in the final analysis, with attendance of 6 (out of 7) sessions defined as achieving minimum adherence.

In some cases, it may be necessary to delay the collection of baseline data for up to 2 months from the point of consent. This may be necessary to facilitate scheduling of physiotherapy appointments for participants allocated to the CMT arm at research sites where there is limited capacity (due to physiotherapist availability) to deliver the intervention.

Table 2: Schedule of assessments

Assessment	Timepoint						
	Screening	Consent	Baseline	Intervention delivery (0-6 months)	6 months	12 months	13-14 months
Eligibility assessment	x						
Participant invitation	x						
Screening data	x						
Informed consent		x					
Data access form		x					
Baseline data and diversity and inclusion survey			x				
WOMAC			x		x	x	
GAKS					x	x	
PCS			x		x	x	
PSEQ			x		x	x	
WPAI-OA			x		x	x	
EQ-5D-5L			x		x	x	
Healthcare resource utilization			x		x	x	
Baseline qualitative survey			x				
Randomisation				x			
Physiotherapy sessions (CMT arm)				x			
Treatment log				x			
Adverse events				x	x		
Death				x	x	x	
Semi-structured interviews							x

If the final data indicates any difference in the rate of knee replacement between the CMT and control arm (see section on Economic Analysis), we will seek further funding to follow participants for a 10-year period. By accessing the HES (Hospital Episode Statistics) database along with the National Joint Registry (NJR), we will obtain data on the numbers of participants in each arm who opt for surgery each year for a period of 10 years after the trial. These data will be combined with data collected during this study. We have communicated our intent to HES and NRJ who are supportive of our plans. Following their advice, we have explicitly stated in the consent materials that NHS number and date of birth will be sent to HES/NRJ so that we can access health information.

8.8 Strategy to maximise trial retention

Baseline:

Once consented to the study, participants will receive an email from the secure trial database with a link to complete baseline outcome questionnaires (or paper booklet, depending on preference) along with a cover letter (see 'Baseline questionnaire cover letter'). They will receive a maximum of three letter/email reminders (see 'Baseline questionnaire reminder letter') to complete these baseline data over a two-week period. If they request to complete outcomes via paper-based questionnaires, they will receive three follow-up calls over a two-week period.

Follow-up:

Following treatment, participants in the CMT arm will be sent an information letter/email explaining next steps of the trial (see 'Group 1 follow up information letter'). Participants in the control arm will also be sent an information letter (see 'Group 2 follow up information letter'). These letters/emails will inform participants of the dates that the follow-up questionnaire will be sent out.

At the two follow-up points, participants will receive a letter/email inviting them to complete outcome data (see 'Six-month questionnaire cover letter' and 'Twelve-month questionnaire cover letter'). For participants who opt to complete outcomes electronically, this letter will be sent via REDCap and contain a link to the online survey to complete outcomes. For those who opt for paper-based outcomes, this letter will be posted with the booklet of questionnaires.

A member of the research team who is blinded to treatment allocation will monitor return of all outcome data. This monitoring will allow the research team to identify missing outcome data and send reminders as appropriate. Reminders for the 6-month and 12-month outcome data will follow the schedule below:

- **At 3 days after the initial invitation to complete outcomes is sent**, if outcome data not completed, a Trial Administrator (or the REDCap system) will e-mail the participant with a reminder to complete outcomes (see 'Six-month questionnaire reminder letter' and 'Twelve-month questionnaire reminder letter').
- **At 1 week after the initial invitation to complete outcomes is sent**, if outcome data not completed, a Trial Administrator (or the REDCap system) will e-mail the participant again with a reminder to complete outcomes.
- **At 2 weeks after the initial invitation to complete outcomes is sent**, if outcome data not completed, a Trial Administrator (or the REDCap system) will e-mail the participant again with a reminder to complete outcomes. A text message will also be sent to the participant, and they will receive a follow-up call from a trial administrator.
- **At 3 weeks after the initial invitation to complete outcomes is sent**, if outcome data not completed, a trial administrator (blinded to group allocation), will telephone the participant to obtain a minimal data set. This minimal dataset will include the WOMAC questionnaire, the GAKS, and the EQ-5D-5L.

If outcome data are unable to be collected post-intervention, this will be recorded in the trial database as missing (lost to follow-up). Participants that do not return the 6-month outcomes will still be contacted for their 12-month outcome data.

Participant newsletter:

In addition to the letter (described above) that participants will receive after they have completed their treatment, we will send a series of newsletters to each participant between 3-11 months after randomisation. We anticipate sending one newsletter every 4-6 weeks, but this exact schedule will be determined through consultation with our PPIE group. These newsletters will be sent via email/letter (depending on participant preference) and will remind participants that they are still in the study, explain the importance of completing the outcomes and give some update on study progress, e.g. numbers of participants who have been recruited. The exact format and content of each newsletter will be developed through ongoing consultation with our PPIE group.

Incentives to complete outcome data

As explained above, all participants, (irrespective of group allocation), will receive £20 when they receive the invitation to complete 6-month outcomes and £20 when they receive the intervention to complete the 12-month outcomes. These payments will be made by bank transfer as this is the only mechanism available to University of Salford staff to reimburse participants.

8.9 Qualitative assessments and evaluation

There will be two components to the embedded qualitative study, both of which will inform our programme theory. The first will focus on understanding the impact of the CMT intervention on daily living, self-management and patient's beliefs around knee OA. Secondly, working with the physiotherapists, we will explore potential barriers and facilitators to delivery and implementation of the CMT intervention within an NHS setting informed by the Normalisation Process Theory (NPT) [34]. NPT will provide a framework to understand how CMT can become routine with current NHS practice by exploring physiotherapist engagement, barriers to implementation, benefits, and sense-making around CMT.

The qualitative work with patient participants will build on our earlier work investigating patient and physiotherapy perceptions immediately after CMT [35]. In this study, we will interview participants 6-10 months after they have completed the intervention to explore longer-term implementation of CMT concepts occurring after exposure to the intervention. To facilitate this work, and minimise the burden on participants, we will use a baseline qualitative survey (see 'Baseline qualitative survey') to capture understanding and perceptions of knee OA pain and views of prognosis before the intervention. This survey will be completed at the same time as the baseline outcomes by all participants. We will then interview a sample of participants in the CMT arm after the 12-month outcome data collection point. These interviews will take place 13-14 months after randomisation, and this will remove the potential for bias in trial outcomes which could result from contact with a qualitative researcher in one arm of the study

We will purposively recruit a minimum of 15 patients who have received the CMT intervention for interview. To be included in the qualitative work, we will invite patients who have a varying attendance recorded (see Section 6.5). Specifically, we will invite participants who have attended four or less sessions (low attendance), those have five or six sessions (medium attendance) and those who have attended all seven sessions

(maximum attendance). By including participants with varying attendance, we will explore what elements of the intervention have been implemented in self-management behaviours and attitudes towards knee OA. These data will be triangulated with outcome scores and baseline beliefs. While we will aim to interview a minimum of 15 participants, the exact number interviewed will be determined by information power through ongoing analysis during the interview period.

Each participant selected for the qualitative work will be invited to attend an online interview. We will provide guidance to help set up the call for those who find it difficult to engage with technology and offer a telephone interview for those unable to use the internet. Through semi-structured interviews, guided by a topic guide (see 'Topic guide (patient interview')) and the baseline qualitative survey, we will gain insight into the participants' personal experiences/opinions of the CMT intervention (usability, adherence, effectiveness, and acceptability) and its influence on their perceptions of knee OA. These questions were co-developed with our advisory panel. The data from the baseline survey will be analysed separately to the interviews. Both the qualitative survey and the interviews will be analysed with template thematic analysis [36] allowing for us to develop coding whilst considering *a priori* themes developed from self-management literature. Template thematic analysis will be appropriate to use for the larger dataset from the survey.

The second part of our qualitative work will be carried out with the physiotherapists who deliver the CMT intervention during this study. Participation in this qualitative work will be optional. For those who consent, we will run a series of online focus groups, including at least three physiotherapists who have delivered their final CMT intervention session within 3 months of the date of the focus group. A qualitative researcher will lead the focus group and, using the topic guide (see 'Topic guide (physiotherapist focus group)'), will explore implementation of CMT, gaining insight into the training course and also exploring barriers and facilitators to implementation of CMT on the NHS. This topic guide has been developed to address core constructs of the NPT. These data will be analysed through framework analysis [37] so we can use a deductive approach and map the data on the constructs of NPT [34]. We can then use an inductive approach to allow for us to capture all the insight into how we can inform an implementation strategy for CMT for the NHS (if the results of the trial support future rollout).

8.10 Withdrawal criteria

Participants will be able to withdraw from the BEPKO-3 trial at any time without affecting the clinical care they receive. However, if participants are in the CMT arm, they will no longer receive the CMT treatment. This is clearly explained in the participant consent form.

If participants do decide to withdraw, they will be provided with two options:

1. Discontinue the intervention: Withdraw from receiving the CMT treatment (if in the CMT arm) but still provide follow-up outcome data at 6 months and 12 months.
2. Complete withdrawal from the trial. If they choose this option, they will not be contacted at the follow-up timepoints. However, their baseline data will be retained.

Any change in participation and/or withdrawal from the study will be clearly documented in the study records.

8.11 End of trial

The end of the study is defined as the return of the final (12-month) questionnaire data from the final participant in the trial or the final interview. The research team at the University of Salford will notify the Sponsor administration team, participating sites, and REC within 90 days of the end of study. The final report required by the REC and HRA will be submitted within 12 months of the end of study.

9 ADVERSE EVENT MANAGEMENT

9.1 Definitions

9.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence involving a participant, which does not necessarily have a causal relationship with the intervention or study.

AEs exempt from formal recording

For the intervention group, common AEs listed below that are identified during or after intervention sessions will be recorded on the treatment log (not an AE form), for clinical purposes only:

- Any accidents (e.g. falls) which occur during normal daily activities
- Exacerbation of pre-existing musculoskeletal conditions (including knee pain) which last no more than five days

Any AEs that are not listed above should be recorded using the AE form (See 'Adverse events form'). Forms should be completed by the treating physiotherapist as soon as possible after becoming aware of the AE and sent to the study team. All AEs should be assessed within 24 hours of identification to check if they constitute a 'Serious Adverse Event' as per section 9.1.2 below. If assessed as a Serious Adverse Event, it should be reported within 24 hours, following the procedures outlined in section 9.2.4.

9.1.2 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence 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
- Intervention is required to prevent one of the above or is an important medical condition

SAEs exempt from reporting:

Any treatment which was elective or pre-planned for a pre-existing condition will not be considered to fulfil the criteria for 'serious' and will not be reported as a SAE for this trial. However, these data will be recorded as part of follow-up data collection in the participant questionnaires.

9.2 Recording Adverse Events and Reporting Serious Adverse Events

9.2.1 Recording and reporting period

Intervention (CMT) group: All AEs and SAEs (unless otherwise specified) occurring from the time of informed consent until the six-month follow-up time-point must be recorded and reported as appropriate. Participants will be asked about anything that might constitute a SAE at the six-month follow-up questionnaire (see 'Adverse event question') and will also be given the opportunity to identify any events at every face-to-face physiotherapy session or via email/letter (sent to the trial team) during the intervention period.

Usual care group: The usual care group will be asked about anything that might constitute a SAE during the six-month follow-up questionnaire only questionnaire (see 'Adverse event question'). It will not be possible to collect a comparison dataset for the usual care group within this period without contaminating usual care. This is a pragmatic study, and the participants will not be contacted during the intervention period, unlike the intervention group. It is important not to contact the usual care group more than is necessary so as not to introduce bias. We anticipate a low risk of adverse events arising from usual NHS care.

9.2.2 Recording and assessing AEs/SAEs

Participants in the intervention group will be asked about any potential AEs at the start of each face-to-face physiotherapy session. In addition, during the session the treating physiotherapist will monitor for any indications of an AE. Potentially AEs will be evaluated by the treating physiotherapist with follow-up contact from the research team to confirm the details. Participants in the intervention group will also be provided with contact details (generic email address and phone number) for the study team. Whilst participants will not be actively encouraged to report AEs via this route, they may seek advice and help from the study team which may result in AEs being disclosed/discussed. Any AEs, with the exception of those listed in Section 9.1.1, will be recorded on the AE form and stored on the secure trial database unless they fulfil the criteria for a 'Serious Adverse Event' in which case they will be reported to the sponsor via the SAE form (see Section 9.2.3 below).

All AEs should be assessed by an appropriately qualified member of the study team within 72 hours of identification to determine if they meet the criteria to be reported as SAEs as defined in Section 9.1.2. If any AEs meet these criteria, they must be reported to the sponsor within a further 24 hours. If the follow-up questionnaire received from a participant indicates events that may fulfil an SAE, then they should be contacted for further information and an SAE form completed if applicable.

All SAEs should be reported to study team (using the document 'Serious Adverse Event Form'), irrespective of their relationship to the intervention unless they are exempt from reporting (see Section 9.1.2). Once received, the study team review the SAE and request further information if required from the treating physiotherapist or participant appropriate.

The causality of SAEs (i.e. relationship to study intervention) will be assessed by the chief investigator and another appropriately delegated member of the trial team using the classifications in Table 5 below.

Table 3: SAE Causal relationships

Relationship to study 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 study intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study intervention). 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.

9.2.3 Expected SAEs

There are no expected SAES previously documented for this intervention. Therefore, any that are assessed as having a causal relationship to the intervention will not undergo expectedness assessment and will be expedited to the REC as per section 9.2.4 below.

9.2.4 Reporting SAEs

The trial team will liaise with the treating physiotherapist/participant to compile all the necessary information. Once the SAE form has been completed, causality assessments will take place as per section 9.2.2 above. SAEs that are deemed possibly, probably or definitely related to the trial intervention by causality assessor will be notified to the REC within 15 days.

9.2.5 Follow-up of reported SAEs

Treating physiotherapists or the study team will monitor for changes to unresolved SAEs through ongoing monitoring during the intervention (treating physiotherapist) or via direct contact with the participant (study

team). If a treating physiotherapist becomes aware of any change of condition or other follow-up information, it should be reported to the study team by completion of another serious adverse event form (indicating that it is a follow-up report) as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached where possible.

9.3 Responsibilities

Table 4: SAE responsibilities

Treating physiotherapists (responsible for delivery of the CMT intervention)	Checking for AEs when participants attends for physiotherapy sessions **1.** Ensuring that all SAEs are recorded and reported to the study team within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that reported SAEs are chased with the study team if a record of receipt is not received within 2 working days of initial reporting.
Chief Investigator/delegate OR Independent clinical reviewer	**1.** Clinical oversight of the safety of patients participating in the study, including an ongoing review of the risk / benefit **2.** Using clinical judgement in assessing causality **3.** Review of all related and unexpected SAEs
Trial team delegate (e.g. Trial manager/Statistician/Lead physiotherapist)	**1.** Central data collection and verification of SAEs, according to the study protocol **2.** Expectedness assessment of related SAEs **3.** Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit. **4.** Reporting safety information to the independent oversight committees identified for the study (Trial Steering Committee (TSC))
Sponsor delegate	Review SAEs that are deemed possibly, probably or definitely related to the trial intervention.

Trial Steering Committee (TSC)	In accordance with the TSC charter, periodically reviewing safety data.

9.4 Notification of deaths

All deaths, when they are identified (up to the 12-month follow-up time-point), will be reported to the sponsor by the study team overseen by the CI, irrespective of whether the death is intervention-related, or an unrelated event. Deaths identified between six and 12 post-randomisation will be recorded for outcomes purposes but will not be classed as an SAE.

9.5 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.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation and attrition

The minimally clinically importance difference in the primary outcome, the composite WOMAC score is 17-22% [38]. This trial is therefore powered to detect a 20% difference between groups in the composite WOMAC score at the primary end point (12 months). In our feasibility study, the baseline mean (SD) of the composite WOMAC score was 41.3 (17.8). A 20% change therefore equates to a change of 8.3 points, which gives an effect size of 0.46. Based on these estimates, 101 participants per group obtains 90% power for a two-sided test with type 1 error (α) set at 5%. Accounting for 20% attrition indicates a target of 126 participants per group.

We have mapped specific initiatives to reduce attrition. These include financial incentives, regular communication to participants through a newsletter and creation of a dedicated outcome data collection reminder schedule. With these additional measures, we are confident we can achieve an attrition rate less than 20%.

10.2 Planned recruitment rate

In our previous feasibility study, we tested the potential to recruit participants using the same inclusion/exclusion criteria as this study. Working with three MSK CATs departments (not physiotherapy departments or GPs), we

were able to randomise a total of 82 participants over a 10-month period. This equates to a recruitment rate of 2.7 per site per month. We have assumed the slightly lower rate of recruitment of 2.33 participants per site per month for this trial. With an 18-month recruitment period, this equates to 252 participants (6 sites x 18 months x 2.33).

10.3 Summary of baseline data and flow of participants

Analyses will be reported in line with the CONSORT statement. Descriptive statistics will be presented to summarise the distribution of baseline variables across each of the two randomisation groups. The continuous baseline variables (age, height, weight, duration of knee pain symptoms) will be reported with means & standard deviations, if shown to be normally distributed, using a combined skewness and kurtosis test, otherwise will be reported with medians and interquartile ranges (IQR).

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of participants:

- Screened for eligibility
- Reason for not being eligible,
- Found eligible,
- Reasons not approached,
- Approached
- Excluded before consent and reason for exclusion
- Consented
- Excluded before randomisation and reason for exclusion,
- Randomised
- Allocated to each randomisation group
- That received each allocated intervention
- That did not receive each allocated intervention
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each analysis group,
- Analysed for each analysis group,
- Not analysed (and the frequency of each reason for not being analysed) for each analysis group.

10.4 Primary outcome analysis

Population: All participants

Treatments: CMT + Usual care vs usual care alone , regardless of non-adherence or receipt of surgery to treat knee OA.

Primary outcome: Mean difference in WOMAC composite score at 12-month follow-up

Handling of intercurrent events

- Failure to complete CMT (attending fewer than 6 out of 7 sessions) – Treatment policy strategy
- Surgery to treat knee OA – Treatment policy strategy

The primary analysis will adopt a treatment policy strategy in line with the ICH E9(R1) estimand framework. All intercurrent events occurring after randomisation, including failure to complete the CMT intervention

(attending fewer than 6 out of 7 sessions) or undergoing knee surgery, will be considered part of the treatment effect. Participants will be analysed in the arm to which they were randomised regardless of these events. The primary outcome will be the adjusted mean difference in WOMAC composite score at 12 months: this will be estimated using a linear multilevel analysis of covariance (ANCOVA) model, including treatment arm (fixed effect), baseline WOMAC as a covariate, and site and receipt of surgery as random effects. The estimate of the difference for the WOMAC composite score between intervention arms will be presented with 95% confidence intervals and p-values: statistical tests will be two-sided. Missing primary outcome data will be replaced using multiple imputation under missing-at-random assumptions, and analyses will be conducted using the Stata MI command.

10.5 Secondary outcome analysis

Secondary outcomes, including those measured at 6-month follow-up, will be analysed using methodology consistent with the primary outcome analysis. All participants will be analysed in the arm to which they were randomised, regardless of adherence to the CMT intervention or receipt of knee surgery, in line with a treatment policy strategy.

The following secondary outcomes will be analysed:

- Composite WOMAC score at 6 months post-randomisation
- WOMAC subscales (pain, function, stiffness) at 6 and 12 months
- Pain Catastrophizing Scale (PCS) at 6 and 12 months
- Pain Self-Efficacy Questionnaire (PSEQ) at 6 and 12 months
- Work Productivity and Activity Impairment Questionnaire (WPAI-OA) at 6 and 12 months
- Health-related quality of life using the EQ-5D-5L at 6 and 12 months

Descriptive statistics will be provided for the Global assessment of knee symptoms (GAKS) at 6 and 12 months to understand differences between the intervention and control.

10.6 Sensitivity analyses

A per-protocol analysis will be carried out, restricted to participants who (a) attended ≥6 of the CMT sessions (applied to intervention arm only) and (b) did not undergo knee replacement prior to the 12-month outcome assessment (applied to participants in both arms). This analysis will address the efficacy of the CMT intervention under ideal adherence conditions.

A complete-case analysis will be performed, including only participants with complete outcome data at baseline and follow-up. This will provide a sensitivity check for the assumptions about missing data inherent in the base-case analysis.

10.7 Interim analysis and criteria for the premature termination of the trial

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated

deviations from the protocol/ regulations). If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

No interim analyses of the outcome data will be undertaken before the final data is collected. However, the TMG/TSC will regularly review recruitment targets at each site. If recruitment is lower than anticipated, at any sites, then additional PICs will be identified, and the number of research sites may be increased.

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

Follow-up reminders and phone calls will be undertaken to minimise the missing outcomes, as described earlier in the protocol. For participants who complete outcomes electronically (using the trial database), there will be no missing data as it is not possible to submit partially completed questionnaires. For participants who complete paper outcomes, missing primary outcome data will be replaced using multiple imputation under missing-at-random assumptions, and analyses will be conducted using the Stata MI command.

10.9 Economic evaluation

An economic evaluation will be conducted to determine the cost-effectiveness of CMT over and above usual care. The primary analysis will be a within-trial analysis, with a 12-month time horizon. We will estimate the costs of CMT and usual care using national average unit costs. Using EQ-5D-5L data from baseline and each follow up point, we will derive quality-adjusted life years (QALYs), serving as the primary health outcome for the cost-effectiveness analysis. The van Hout algorithm will be used to estimate QALYs from the EQ-5D-5L, as recommended by NICE [39, 40]. Unit costs will be sourced from established databases, such as NHS Reference Costs [41] and PSSRU Unit Costs of Health and Social Care [42]. Costs of the intervention will be calculated, incorporating the cost of training, delivering the sessions, and the associated materials, and compared with the usual care group. The primary analysis will adopt an NHS and personal social services perspective, while a secondary analysis will be carried out from a wider societal perspective. Missing data will be imputed using the same methods as described in section 10.9 above, with the imputed results used for the based case, and a complete case analysis conducted as a sensitivity analysis.

Additionally, as a sensitivity analysis, QALYs will be estimated directly from the WOMAC, using a published mapping algorithm [43] for knee OA. Significant differences in the quality-of-life values estimated directly from the EQ-5D-5L and those estimated from the mapping of the clinical instrument can help to identify patterns of quality-of-life gain that may not be captured by a generic quality of life instrument.

If the trial identifies significant differences between the intervention and control arm, either in QoL (EQ-5D-5L) or rate of knee replacement, a second analysis will be conducted, using a lifetime horizon, to extrapolate the potential longer-term impacts of the intervention. Building on this analysis, we will apply for additional funding to monitor participants through the HES (Hospital Episode Statistics) database. Combining these data on knee surgery with trial data, we will quantify the numbers of participants in each arm who opt for surgery each year for a period of 10 years after the intervention. We have specified our intent to carry out this long-term follow-up in the participant information sheet and added a specific statement on the consent form.

11 DATA HANDLING

11.1 Data collection processes

A secure and auditable trial database will be created using the REDCap platform and used to store all clinical data for the study. This database will be built and hosted by Northern Care Alliance (NCA) and will be a web-based application. The database will enable customisable user rights to restrict data entry, export or viewing and will incorporate full audit trials to log user activity and data input. The system will be configured to comply with NHS Digital Data Security & Protection Toolkit (DSPT) requirements, ICH-GCP recommendations and 21 CFR Part 11 (US FDA electronic records standard). To meet these requirements, the system will incorporate full audit trails, role-based access, and two-factor authentication.

Entry into the database will be either from participants themselves or via transfer of data collected by study staff from paper questionnaires or following telephone call by study staff. Details of adverse events will be entered by the trial manager. Data on KL-grade (radiographic severity) will also be entered into the trial database by the trial manager.

Clinical records and treatment logs for participants who receive the CMT treatment will be stored on a secure digital platform, Microsoft OneDrive, which will only be accessible by the lead physiotherapist (or physiotherapist responsible for monitoring intervention fidelity) and the treating physiotherapists. To facilitate this, we will provide each physiotherapist with a University of Salford registered laptop device.

Screening data on eligibility criteria along will be stored on a password protected file with the secure Microsoft OneDrive environment. Contact details for participants, including GP contact details, will be stored on another password protected file with the Microsoft OneDrive environment. All consent forms and data access forms will be scanned and stored electronically. Access to documents which contain personal data (e.g. name and contact details) will be managed by the CI and trial manager.

11.2 Audio data and video data

Interviews will be recorded and transcribed using Microsoft Teams if performed via video conference or audio recorded if carried out over the phone. Once the interview has been transcribed and confirmed as accurate, the recordings will be destroyed. Interviews will be conducted using a password-protected computer provided by the University of Salford. This device will be stored at the University when not in use. Once transcribed, all data will be completely anonymised.

We may record video data for the purposes of intervention monitoring, including fidelity assessment. These videos will be collected using Microsoft Teams on a University of Salford laptop (with external webcam) that the physiotherapist will have access to for the duration of the study. All video data will be stored in the secure OneDrive environment. The videos will be assessed within two weeks of the original recording being made and then permanently deleted. Data obtained from these videos will be completely anonymised.

11.3 Data access and security

All collected data will remain anonymous. The only link between this number and participant ID will be via the consent form. All data will be transferred from a paper sheet (if appropriate) to electronic files within 1 week of data collection and the original paper copy destroyed. As explained above, trial data will be stored in the secure trial database and all other data stored in a secure Microsoft OneDrive environment.

114 Archiving

On completion of the study, we will contact participants to provide a summary of the findings (within 1 year of study completion). Once this summary has been sent out, we will permanently delete all personal data with the exception of NHS number and date of birth. NHS number and date of birth will be retrained for 10 years (in those who provide consent) so that we can obtain data on knee replacement surgery from NJR/HES. After this 10-year period all personal information will be deleted.

Once all outcome data has been collected the trial data will be transferred from the REDCap trial database to a secure server at the University of Salford. These data will be fully anonymised and stored for a minimum period of 10 years. Individual-level (fully anonymised) outcome data will be made available with the final publication. However, we will not provide individual-level data on comorbidities, religion, socio-economic status or ethnicity.

It will be the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 10 years after the end of study, and in accordance with national legislation. The research team will notify sites when study documentation held at sites may be archived and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

12 MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor may visit the participating sites to conduct audits/ inspections.

Monitoring and source data verification will be conducted by trial manager and study statistician. The extent and nature of monitoring will be determined by the study objectives, purpose, design, complexity, blinding, number of participants and sites, and endpoints. Audits will be conducted by the Sponsor according to their audit plan; these may be central or site audits.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Assessment and Management of Risk

This study has been risk assessed by the Sponsor according to their Standard Operating Procedures (SOPs). A full risk assessment has been by the study team to identify any risks and mitigating actions, which have fed into the study design and development of the protocol.

13.2 Peer review

This study has been funded by the NIHR as has been peer reviewed by an NIHR committee and five external referees as part of the application process. The protocol has been reviewed by the TSC prior to submission for REC approval.

13.3 Public and Patient Involvement and Engagement (PPIE)

We have formed a PPIE group, consisting of five patient representatives who will advise on research design, participant information resources and dissemination. Input from this group helped shaped the original grant application and informed the development of this protocol. Our PPIE groups carried out an extensive review of participant information resources (e.g. participant information sheets, advertising materials) for the study prior to submission for REC approval. During the study, PPIE members will attend regular meetings to advise on progress, help the team deal with recruitment issues and inform the creation of information resources used to minimise attrition (e.g. participant newsletters). This group will also advise on dissemination of the study findings. The lead PPIE member will also attend TMG meetings (where possible) and attend TSC meetings.

13.4 Research Ethics Committee (REC) & Regulatory Considerations

The study described in this protocol is developed from two previous studies, the first a training development study and the second a feasibility randomised controlled trial and integrated qualitative study. REC and HRA approval was granted for both these studies (REC Refs: 21/EM/0225 and 21/WM/0255) and (IRAS Project ID 298932 & 306258).

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki and the UK Framework for Health and Social Care Research. The protocol and all related documentation (e.g. informed consent form, participant information sheet, questionnaires) have been reviewed approval by a Research Ethics Committee (REC) and Health Research Authority (HRA). Participant activities must not begin until approval from the HRA and REC has been obtained and documented.

The University of Salford is responsible for notifying the REC of the end of study within 90 days. Within one year of the end of study, the Sponsor will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enrol a participant into the study confirmation of capacity must be sought from the site's research and development (R&D) department.

13.5 Amendments

If changes to the study are required these must be discussed with the Sponsor, who is responsible for deciding if an amendment is required and if it should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval, and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant

approvals are in place. All amendments must be notified to participating sites prior to implementation.

13.6 Protocol Compliance & Non-Compliance Reporting

The Principal Investigator at each site is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable, however accidental protocol deviations (non- compliances) may happen and as such these must be reported to the trial manager. All non- compliances should be reviewed and assessed by the trial manager and chief investigator to determine if they meet the criteria of a 'serious breach'. Non-compliances which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

A 'serious breach' is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study; or
- The scientific value of the study.

If a serious breach is identified the University of Salford be notified immediately (i.e. within 1 working day). The report will be reviewed by the trial manager and CI and, if appropriate, they will notify the REC within 7 calendar days of being made aware of the breach.

13.7 Data Protection and Patient Confidentiality

The study will be conducted in accordance with the Data Protection Act 2018. All investigators will ensure that participant's anonymity is maintained throughout and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form, data access form and enrolment log) only by the participants study specific identifier. This includes both electronic and paper documents. Participants' contact details will be recorded and stored securely by the trial manager for the purposes of administering the follow up questionnaires. This includes their name, address and/or email address and telephone number. Access to this will be restricted to the members of the study team who require this to fulfil study requirements.

Transcripts from recordings will be anonymised, transcribed and then recordings deleted within 2-4 week of the original recording.

The Chief Investigator will act as the custodian of the data generated in the study.

13.8 Indemnity

The University of Salford is acting as the research Sponsor for this study and will provide indemnity cover for the study. This indemnity cover will legal liabilities which arise due to negligence. Non-negligent harm is not covered by the indemnity scheme.

13.9 Access to Final Study Dataset

A fully anonymised dataset (excluding interview transcripts) will be made available with the final publication. This dataset will include only summary (group-level) descriptors of comorbidities, religion, socio-economic status and ethnicity to ensure there is no possibility of participants being identified from published data.

Anonymised transcripts may be made available to other researchers (including those outside of the Universities) by controlled access if they secure the necessary approvals for purposes not related to this study, subject to consent from participants.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

As the Sponsor, the University of Salford will own data and results arising from the study. On completion of the study, a final study report will be prepared and shared with the NIHR as the Funder of the study. A report will also be shared with REC per the conditions of favourable opinion.

In all outputs, the Funder and Sponsor will be duly acknowledged. We anticipate several academic outputs from the BEPKO-3 trial. We will publish a protocol paper, a paper describing the findings of the trial, another paper reporting on the economic evaluation, along with a paper reporting on our qualitative evaluation. We will ensure that all journal papers are compliant with the NIHR open access policy.

We will present the findings of our clinical study at the international meeting of the OA Research Society International (OARSI). To reach out to health professionals within the UK, we will present our findings at the Physiotherapy UK annual conference. We will also actively engage with national and international experts in this field via research exchange visits, social media channels and through a webinar which we will run when we submit the work for publication. Our primary reason to engage other academics would be to motivate others to run future RCTs to investigate CMT in different settings if finding from this study demonstrate clinical effectiveness.

If the data from this trial support CMT as a treatment for knee OA, we will also create a network of trainers across the UK which will enable us to upskill the NHS physiotherapy workforce to deliver the CMT intervention. We will then work with NHS trusts to pilot the intervention. As part of this work, we will collect anonymised pain data from all participants who receive the intervention. Combining these data with the trial data will create a stronger case for widescale uptake of this intervention across the NHS.

Each participant in the trial will be sent a written summary of the research findings on study completion. We will also engage with patients who suffer with knee osteoarthritis by writing articles for magazines, such as Arthritis today, and communicate actively with the Arthritis Foundation, who provide information and resources for people who live with arthritis.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be determined as per the criteria outlined the International Committee of Medical Journal Editors.

15 DECLARATIONS OF FINACIAL CONFLICT OF INTEREST

No investigators, members of the trial management group or members of the trial steering committee have any financial conflicts of interest to declare.

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17. APPENDICIES

Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	5		Stephen Preece	Modification of the Global assessment of knee symptoms outcome and clarification of when this will be collected. Addition of collection date of birth at the point of consent

Detail all protocol amendments. Protocol amendments must be submitted to Sponsor for approval prior to submission to the REC.