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The East Midlands Knee Pain Multiple Randomised Controlled Trial Cohort Study: Cohort Establishment and Feasibility study protocol

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ABSTRACT

Introduction: Knee pain and osteoarthritis (OA) are a common cause of disability. The UK National Institute of Health and Care Excellence (NICE) OA guidelines recommend education, exercise and weight-loss advice (if overweight) as core interventions before pharmacological adjuncts. However, implementation of these in primary care is often suboptimal. This study aims to develop a complex intervention with non-pharmacological and pharmacological components that can be delivered by nurses. The feasibility and acceptability of the intervention, and feasibility of undertaking a future cohort-randomised controlled trial (RCT) will be explored. .

Methods and analysis: In phase 1, we will develop a training programme for nurses and evaluate the fidelity and acceptability of the non-pharmacological element of the intervention. Fidelity checklists completed by the nurse will be compared to video-analysis of the treatment sessions. Patients and nurses will be interviewed to determine the acceptability of the intervention and explore challenges to intervention delivery. The non-pharmacological component will be modified based upon the findings. In phase 2, we will assess the feasibility of conducting a cohort RCT comprising of both the pharmacological and modified non-pharmacological components. We will compare three groups: group A will receive the non-pharmacological components delivered before pharmacological components; group B will receive pharmacological components followed by the non-pharmacological components; and group C (control arm) will continue to receive usual care. Study outcomes will be collected at 3 time points: baseline and weeks 13 and 26 after randomisation. Qualitative interviews will be conducted with a sample of participants from each of the two active intervention arms.

Ethics and dissemination: This protocol was approved by the East Midlands-Derby Research Ethics Committee (18/EM/0288) and registered at clinicaltrials.gov (NCT03670706). The study will be reported in accordance with the CONSORT guidance and standards. The results will be submitted for publication in peer-reviewed academic journals.

CllinicalTrials.gov: NCT03670706.

KEYWORDS

Feasibility, Complex intervention, Knee pain, Osteoarthritis, Nurse-led care, exercise, Weight-loss, Education, Analgesia

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to develop and evaluate the feasibility of a wholly nurse-led intervention following the core NICE guidelines for treating knee pain and OA.

- This study will not determine the effectiveness of this model of care for knee pain and OA, but will explore the feasibility of implementation and running an adequately powered randomised-controlled trial (RCT) and determine signal of effiacy.
- Assessing fidelity of intervention delivery will allow us to explore the extent to which the nurses can deliver individual components of the complex package of care as planned, and alongside exploring its acceptability will inform refinements to nurse training and/or the package of care.
- Blinded outcome assessment.
- Participants and nurses delivering care will not be blinded to each intervention, but the use of cohort RCT study design will minimise bias associated with pragmatic RCTs.

INTRODUCTION

Knee pain affects one in four people aged over 55 years when it is most commonly caused by osteoarthritis (OA).[1] The global prevalence of symptomatic knee OA is estimated at 4%, and it has an important impact on both affected individuals and health and social care systems.[2, 3] The socio-economic and healthcare burden of knee OA is likely to increase due to the ageing population and obesity epidemic.[2, 4]

Best practice guidelines for managing OA published by the National Institute for Health and Care Excellence (NICE) recommend individualised patient education, advice and access to information about OA and its management, strengthening and aerobic exercise, and guidance on losing weight if applicable as core treatments, with consideration of adjunctive pharmacological and other non-pharmacological treatments as required.[5] However, core treatments are frequently under-utilised as both doctors and patients predominantly focus on pharmacological options including opioids.[6, 7] Most people with OA feel they do not receive the treatment they need from general practitioners (GP), with an overemphasis on prescription drugs and lack of discussion about exercise and diet.[8] Given the growing concerns about the overuse of opioids for musculoskeletal pain including OA [9] it is important to explore alternative models of healthcare delivery with an emphasis on non-pharmacological interventions for this condition.

Alternative models for implementing OA care have shown potential. The MOSAICS trial explored the effectiveness of delivering an enhanced initial consultation with GP and provision of nurse-led follow-ups as a clinically practicable way of implementing NICE guidelines compared to usual care.[10] However, only 29% of patients in the intervention arm reported having a consultation with a nurse, making it difficult to determine whether a nurse could help deliver the core NICE recommendations. Others have included using community physiotherapists and pharmacists for delivering interventions but have only demonstrated short-term improvements in health outcomes.[11]

The majority of patients with knee pain self-manage their symptoms, and those who seek healthcare, are managed by their GPs and community physiotherapists in the first instance.[8] A potential role for practice nurses has been identified [12] and nurse-led clinics already exist for patients with long-term conditions such as coronary heart disease,[13] heart failure,[14] and diabetes[15] resulting in equivalent or better outcomes for patients compared to usual GP-led care. Upskilling practice nurses to deliver the management of long-term conditions is recognised as a key strategy for the future of primary care.[16] This paper describes the protocol for developing and testing the feasibility of a wholly nurse-led intervention for people with knee pain, delivering the core NICE recommendations.

Aims and objectives

The overall purpose is to develop and test the feasibility of a nurse-led intervention for people with knee pain. This study has two phases:

Phase 1 involves the development and evaluation of the non-pharmacological treatment component. Specific objectives are to: [1] develop a training package for nurses to deliver the core non-pharmacological and pharmacological principles to manage knee OA as recommended by NICE; [2] determine the fidelity of delivery of the nurse-delivered components of the intervention; [3] explore patient and nurse acceptability of the non-pharmacological components of the intervention.
Phase 2 will [4] test the feasibility of a definitive randomised controlled trial of nurse-led versus usual care of people with knee pain and [5] explore whether such a trial should provide core analgesia before non-pharmacological interventions.

METHODS

Participants

Participants eligible for both phases of the study will be aged over 40 years and with self-reporting knee pain on most days of the previous month and of at-least three month duration. Knee pain severity will be scored between 4-7 on a 0-10 numeric rating scale. This will be assessed using the following question “Over the past 4-weeks, how intense was the average pain or aching in your knees on a 0-10 scale, where 0 is no pain and 10 is pain as bad as could be?”

Exclusion criteria include participants who are unable to communicate in English, who are housebound or care home residents, on dialysis or home oxygen, pregnant or have dementia, serious mental illness, terminal cancer, autoimmune rheumatic diseases, asthma or lung disease requiring regular daily oral corticosteroids, unstable angina or heart failure, known peripheral vascular disease, stroke with residual weakness or sensory loss, physician-diagnosed peripheral neuropathy with sensory or motor deficit, previous knee or hip replacement, on a waiting list for a knee or hip replacement.

Nurses who undergo the intervention training and delivered the intervention in the study will be recruited to the qualitative components of the study and will give their consent to be interviewed in both phases of the study.

Recruitment

There are three routes of recruitment:

1. Participants will primarily be recruited from the Investigating Musculoskeletal Health and Wellbeing (IMHW) survey (NCT03696134), a cohort study that aims to measure and characterise the development and progression of pain, frailty and disability and form a longitudinal context for nested research. Participants who self-report knee pain as their predominant body pain and consent for future research contact will be sent a questionnaire enquiring about their knee pain, mood, function and quality of life. They will also be asked about willingness to receive information about trials on knee pain, complete further questionnaires on knee pain, and for their data to be used for comparisons with other

participant groups in research studies. Those willing and meeting the eligibility criteria will be invited to take part in the current study (figure 1).

2. Additional participants identified by screening of GP records for previous consultation for knee pain will be sent a questionnaire as outlined above.
3. Finally, people with knee pain or OA who have taken part in previous community-based surveys in Academic Rheumatology, University of Nottingham and consented for future research contact may be approached with a questionnaire.

Setting

Study visits for research assessment will occur at Academic Rheumatology, City Hospital Nottingham, UK and the David Greenfield Unit, Queen's Medical Centre, Nottingham, UK. The intervention will be delivered at Academic Rheumatology, City Hospital Nottingham.

Consent and withdrawal

All participants will give written informed consent before entering the study and before any assessments or interventions related to the study are undertaken. Optional consent will be sought for video-recording of the intervention sessions to evaluate fidelity and audio-recording of participant interviews. Participants will be free to withdraw at any time. In the event of withdrawal, any data collected up until that point will be kept and potentially included in any analyses.

Patient and Public Involvement (PPI)

The design of this study was supported by a patient advisory group. Patients recognised the challenges of providing full explanations and individualised advice in a time-limited GP consultation and agreed that a wholly nurse-led intervention would be acceptable or preferable to most people. They provided input into the content of the both components, the number and length of intervention sessions and the use of exercise diaries.

PHASE 1: DEVELOPMENT OF THE NON-PHARMACOLOGICAL COMPONENT

The non-pharmacological intervention will be developed according to the Medical Research Council (MRC) framework for developing complex packages of care.[17] It was informed by several strands of evidence including current guidelines, an expert multi-disciplinary team of physiotherapists, rheumatologists and nurses, patient opinion, physiological considerations and behaviour change theory.

In brief, the intervention consists of a holistic assessment of the participant, individualised education about OA, aerobic and strengthening exercises and weight loss advice if required. Evidence-based strategies to motivate participants and support adherence to healthy behaviours will be employed.

The training package

A training package for nurses will be developed and piloted during this phase. The content will be based on current NICE guidelines for the management of OA [5] and a report by Arthritis Research UK on the educational needs of health professionals working with people with OA.[18] Academic and clinical experts and members of a PPI group have provided input into the training package.

Delivery of the training package will be underpinned by educational theory [19] and will build on the nurses existing knowledge of the condition. Training will be delivered in face-to-face sessions, complemented by a range of learning resources including a manual, case-studies, online resources and patient simulations. Key components of the training will include:

- The epidemiology and nature of knee pain and knee OA
- Assessment of the patient with knee OA
- Core NICE guidelines for managing OA
- Principles of strengthening and aerobic exercise prescription for knee OA
- Information and advice to support weight loss
- Strategies to support behaviour change
- Pharmacological management of OA and knee pain following a step-wise protocol of optimising analgesia

Study design

A pre-post intervention study using mixed quantitative and qualitative methods to determine the fidelity of delivery and the acceptability of the intervention by patients and nurses. After the nurse training, 20 participants with knee pain will be recruited to this study. They will receive the non-pharmacological components of the intervention covering as described above in four sessions over a five-week period.

Quantitative methods

Fidelity of delivery refers to the assessment of whether content of the sessions were delivered as intended. This will be assessed using a priori fidelity checklist. All interventions in this phase will be video-recorded (with consent). Nurses will self-complete the checklist after each session and a researcher will independently complete the checklist using the video recordings. The individual components of each session will be rated as being done, partially done, not done or not applicable. A sample of videos recordings will be reviewed by a second researcher to determine inter-rater reliability.

Quantitative analysis

Fidelity scores will be presented as the percentage of specified components that were delivered as intended for the overall delivery of the intervention and for individual components.
Inter-rater reliability between the two researchers scoring the video-recordings will be reported, as will the level of agreement between nurse-completed scores and research-completed (video) scores. For

delivery of complex interventions such as this, levels of fidelity have been previously interpreted as 'high' fidelity where 80-100% of the specified components were delivered as intended, 'moderate' 51-79%, and 'low' 0-50%.[20] Where the fidelity scores are less than 80%, we will explore further to establish which components are responsible.

Qualitative methods

Acceptability of the intervention will be explored in a face-to-face interview with all participants who received the intervention. Participants who withdraw from the intervention will be offered the opportunity to take part in an interview to explore their experiences and reasons for discontinuation. The nurses who deliver the intervention will also be invited to interview, to explore their views on the training, experience in delivering the intervention, and perceived factors influencing the fidelity of delivery. All interviews will be audio recorded and transcribed verbatim by an external specialist company Transcribe It® and anonymised.

Qualitative analysis

After data transcription, all data will be checked for accuracy before transcripts are imported to NVivo 12. Qualitative data will be analysed using a Framework approach.[21] This method sits within the broad family of thematic analysis, but is particularly useful for research that has specific questions and a priori issues that need to be dealt with.[22] The analysis will follow the five stages of Framework analysis: familiarisation with the data, construction of an initial thematic framework, indexing and sorting the data using initial thematic framework, finalisation of thematic framework, summarising and displaying the data into a matrix. Emergent themes and subthemes will be discussed and agreed by at least two researchers to increase the validity of the analyses.

Following the fidelity evaluation and qualitative interviews, modifications may be made to study materials, procedures or protocol, and/or nurse training.

PHASE 2: FEASIBILITY COHORT RCT

Trial design

This will be a single centre, mixed-methods feasibility cohort RCT. Participants will be recruited as described above and randomised to one of 3 treatment arms (figure 1).

Group A will receive the non-pharmacological protocol for 13 weeks followed by the pharmacological protocol between weeks 13 and 26 as required,
Group B will receive the pharmacological protocol in the first 13 weeks followed by the non-pharmacologic protocol between weeks 13 and 26 with optimised background analgesia.
Group C is a control (cohort) group and will continue to receive usual care.

Randomisation and allocation concealment

Participants will be individually randomised on a 1:1:1 ratio using randomly permuted block sizes of 3 and 6, stratified for the number of eligible knees (i.e. unilateral or bilateral knee pain). Randomisation codes will be generated by the study statistician. Allocations to groups will be enclosed in serially numbered, opaque, sealed envelopes with a carbon copy paper. The serially numbered opaque envelopes will be packaged and prepared by an independent member not belonging to the research team. Participants will be randomised by the trial coordinator who will ensure that the envelopes are opened sequentially, and only after the participant's name and other details are written on the outside of the appropriate envelope.

Blinding

It is not possible to blind the study participants or the nurse delivering the intervention to the group allocations. However, study personnel involved in outcome assessment and data analysis will be blinded. Participants will be requested not to disclose group allocation to the outcome assessor, but if this does occur it will be recorded. Only once data has been cleaned and analysed will the treatment allocation be made known.

INTERVENTION

Non-pharmacological component

The non-pharmacological component will be delivered by a nurse as detailed in table 1 incorporating any modifications made following the development phase. It will be delivered in up to six face to face sessions over 13 weeks. Participants will continue their usual analgesics in this period.

Table 1 Content of non-pharmacological component of intervention

Content of non-pharmacological component	Session 1	2	3	4	5	6
Assessment						
Holistic assessment including symptoms, pain elsewhere, co-morbidities, impact on function, occupation, mood, sleep, illness perceptions, current levels of PA, and attitudes to PA and weight loss (if required)	✓					
Physical assessment of knee range of movement, lower limb muscle strength, gait and functional activities, BMI.	✓					
Education & Advice						
Provision of ArthritisResearchUK booklet "Osteoarthritis of the knee"	✓					
Nature of Osteoarthritis	✓					
Adverse illness perceptions addressed	✓					
Core treatments	✓					
Benefits of exercise and PA	✓					
Pacing	✓					
Benefits of weight loss (if required)	✓					
Use of heat and cold for pain,	✓					
Appropriate footwear, use of walking aids	✓					
Signposting to further information if required	✓					
Review of above if required		✓	✓	✓	✓	✓
Exercise (individualised programme)						
Strengthening exercise	✓					
Aerobic exercise/ PA	✓					
Functional exercises	✓					
Stretching exercises	✓					
Review performance of exercise		✓	✓	✓	✓	✓
Progression/regression of exercises		✓	✓	✓	✓	✓
Weight loss (if required)						
Previous efforts to lose weight discussed	✓					
Strategies for weight loss discussed	✓					
Agree weight loss goal (5% body weight)	✓					
Signposting to resources (weight loss groups, NHS weight-loss plan)	✓					
Review of weight-loss progress and advice		✓	✓	✓	✓	✓
Adherence/behaviour change strategies						
Patient goals and action plan recorded for exercise and weight loss	✓	✓	✓	✓	✓	✓
Patient's confidence to achieve goals discussed and recorded	✓	✓	✓	✓	✓	✓
Barriers and facilitators discussed	✓	✓	✓	✓	✓	✓
Exercise diary completed and discussed	✓	✓	✓	✓	✓	✓

PA, Physical activity; BMI, Body Mass index.

Pharmacological component

The nurse will take a history of current symptoms, co-morbidities, medications and the main knee complaint of the participant. They will be advised by the nurse to continue on their current analgesia prescribed by their GP, and to add in simpler and safer analgesics in the sequence shown in figure 2. Once they are on a simpler and safer analgesic, they will be advised to reduce the dose of potentially more toxic or stronger analgesic. However, this will depend on the subjective improvement the participant experiences with simpler analgesic. Relative and absolute contra-indications will be assessed against a checklist developed from the British National Formulary (BNF). Participants with absolute contraindication to an analgesic will not be prescribed that drug. Participants with relative contraindications may be prescribed the aforementioned drug if they are willing to do so after exploring risks and benefits. Analgesics will be reviewed at two-weekly intervals over a 13-week period and optimised if the pain relief is insufficient. This will be done over the phone, or at a face-to-face visit, depending on participant preference. The visits and telephone consultations will be conducted by the nurse and prescriptions signed by the principal investigator or nominated deputy. Once a participant achieves adequate pain control and does not request any further changes to their analgesia, they will be advised to contact the nurse by phone for changes to their treatment if needed during the study.

Usual care

Participants allocated to this group will continue to receive usual care for their knee pain. They will not undertake any of the clinical assessments and will not receive any input from the nurse. People in this group will be part of the IMHWS cohort and will not be aware of the content of the invention groups.

Study Outcomes

Feasibility outcomes

The feasibility of running a full trial will be assessed by recording the following data:

- Recruitment rates
- Dropout rate and reasons for drop-out
- Number of scheduled nurse appointments attended
- Number of instances of unblinding
- Completeness of questionnaire data
- Concordance with exercise assessed using data from participants' exercise diaries (total number of days on which exercises were performed)

Participant-reported measures

A summary of all participant outcomes to be collected at 0, 13 and 26 weeks for groups A and B are presented in table 2 and in the online supplementary file.

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Table 2 Summary of questionnaire and research measures to be collected

Domain	Data Source	Measure / Instrument	Time points (week)
Demographic characteristics	Research assessment	Age, height, weight	0 0,13,26
Comorbidities & medications	Research assessment	Comorbidities, current medications	0 0,13,26
Radiographic evaluation	Research assessment	Bilateral knee radiographs: PA semi-flexed weight-bearing and skyline views [23] scored for Kellgren and Lawrence grades and using the Nottingham line drawing atlas [24]	0
Knee Pain	Self-report	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [25]	0,13,26
	Self-report	Analgesic and NSAID consumption	0,13,26
	Research assessment	Quantitative sensory testing† including pressure pain detection threshold, temporal summation and conditioned pain modulation	0,13,26
Physical Activity	Self-report	International Physical Activity Questionnaire (IPAQ) [26]	0,13,26
Function	Self-report	WOMAC function subscale [25]	0,13,26
	Research assessment	Timed Up and Go (TUG) test [27] 30-second chair stand test [28]	0,13,26
Muscle Function	Research assessment	Isometric and isokinetic quadriceps strength†	0,13,26
Quality of life	Self-report	The Short Form (36) Health Survey V2 [29] EQ-5D-5L™ [30]	0,13,26
Psychological wellness	Self-report	Hospital Anxiety and Depression Scale (HADS) [31]	0,13,26
Healthcare use	Self-report	Service use questionnaire to assess use of NHS or private healthcare, prescription and over-the-counter medicines related to knee pain outside of the study	0,13,26
Participant engagement in treatment	Nurse completed questionnaire	Pittsburgh Rehabilitation Participation Scale(PRPS) [32]	13/26*
Exercise adherence	Self-report	Adherence to Exercise Scale for Older Patients (AESOP) [33]	13/26**
Acceptability of intervention	Self-report	Participant satisfaction with treatment	13,26
Blood markers	Research assessment	Non-fasting serum cholesterol, HbA1c and C-reactive protein	0, 26
Safety	Case Report Form	Adverse events	26

* This will be completed by the nurse after each of the non-pharmacological sessions.

** This will be completed by the participant at the end of non-pharmacological arm.

† further description included in detailed in the Supplementary file1

Group C will receive a questionnaire at week 26, enquiring about healthcare utilisation, demographic characteristics, self-reported height, self-reported weight, current alcohol intake and smoking status, comorbidities, medications, joint pain, central aspects of pain in knee scale, WOMAC, SF-36v2, and HADS.

Acceptability of the intervention

Qualitative interviews will be conducted after the intervention (week 26) with approximately 10 participants from each of the intervention arms (Group A and B). They will be purposively selected to represent those with likely low- and high-concordance with the exercise advice using the AESOP questionnaire. Interviews will explore participants' overall satisfaction with the intervention and the sequence of treatment, perceptions of nurse-led care and previous treatment experience, level of adherence to the advice, perceptions of managing their knee pain, as well as perceived impact of their knee pain on their daily life before and after the intervention. Participants who withdraw from the intervention will be offered the opportunity to take part in an interview. Interviews will also be conducted with the study nurses to explore their experience in delivering the intervention, perceived effectiveness of the intervention and barriers to implementation and how these may be overcome.

Safety and adverse events (AEs)

This study intervention follows current NICE guidelines that might offered as part of routine clinical care. As such the risk of severe or unexpected adverse events in low.[34] Exercise and an increase in physical activity may initially increase the risk of adverse events such as pain, fatigue or muscle soreness or increased falls through increased activity. To reduce the risk of adverse events the exercise programme will be tailored to the abilities of the participants. All AE serious and non-serious will be monitored and recorded through the study by the nurses and will be managed in line with current NIHR guidelines.[35]

Sample size

Quantitative study

As this is a feasibility study, a formal sample size calculation for between group comparisons of primary clinical outcome is not appropriate. A target sample size of 53 participants per arm will be sought over the recruitment period to reliably estimate the feasibility outcomes relating to recruitment and retention rates to inform a fully powered RCT. With a sample size of 159 (53 participants per arm), we will be able to estimate a drop-out rate of no more than 20% to within 7% points of the true value with 95% confidence.

Qualitative study

Target recruitment will be 20 participants, ten from each intervention arm. However, final numbers will be determined by data saturation, where no new themes are identified.

Data analysis

Feasibility outcomes will be estimated using descriptive statistics (with 95% confidence intervals) and will be presented overall and per randomised groups. A CONSORT diagram will summarise the flow of participants through the study. Reasons for non-eligibility, withdrawals and non-completion of follow-up questionnaires will be presented if available.

Quantitative analysis

The main quantitative analysis will be of the trial feasibility outcomes:

- Recruitment rate (per month, per recruitment source, per 100 participants approached)
- Dropout rate (per arm, per stage pharmacological/non-pharmacological)
- Attendance rates for scheduled nurse appointments
- Missing data
- Power and sample size calculation for a definitive trial will be based on WOMAC summated knee pain domain scores in the most painful knee at week 26.

Descriptive statistics will be presented for demographic data and all baseline clinical outcome measures. Exploratory analysis of clinical outcomes will be conducted according to randomised groups but will not be interpreted in terms of effectiveness. The emphasis will be on confidence intervals of effect size estimations rather than the p-values. Changes in clinical and patient-reported outcomes from baseline to 13 and 26 weeks will be analysed using appropriate parametric or non-parametric statistics. A comparison of those receiving the pharmacological component first with those receiving the non-pharmacological component first will help determine the order of delivery in a future trial.

Qualitative analysis

Interview data will be analysed following the framework approach [36]. Analysis will be conducted in parallel with the interviews and initial results will inform subsequent sampling and areas of interest to follow-up.

DISCUSSION

People with knee OA continue to often receive suboptimal fragmented care and the core NICE recommendations are under-utilised in primary care.[37] Given that knee pain is common, and there is a huge time-pressure on GPs in the UK, it is vital to find out if a complex package of care incorporating the core recommendations can be delivered by other healthcare professionals such as practice nurses.

We believe that a wholly nurse-led management programme where a nurse acts as the point of contact for people with knee pain due to OA, educates them about the condition, provides core pharmacologic and non-pharmacologic treatments, and builds a long-term therapeutic relationship is

likely to be clinically effective and cost-effective in improving quality of OA care as demonstrated for other chronic conditions.[15, 38-41]

This study will not provide an answer as to the effectiveness of a wholly nurse-led intervention for OA and knee pain, but will determine the feasibility of implementing this model of care and of testing it in a full trial using practice nurses. Assessing fidelity will play an important part in the development and evaluation of the intervention, by exploring the extent to which the nurses can deliver individual components of the complex package of care for knee pain as planned. Combined with qualitative interviews to explore their acceptability, this will provide insight into the suitability of the training and intervention to inform appropriate refinements to the whole package of care that can be tested in a full trial. Although the intervention will take place in a research setting rather than primary care, the study outcomes will provide insight into the feasibility of implementation into real-world practice.

Further, this study will explore at what point analgesia should be optimised within this complex package of care. Having two intervention groups, one where analgesia is provided before the non-pharmacological component and one where it is provided after, will help us determine whether patients exercise better when analgesia is optimised first, or whether they are able to exercise sufficiently before this. This will inform the order of treatment in a two-arm full trial.

The usual double blind placebo-controlled RCT cannot be utilised when investigating the efficacy of complex interventions for knee pain as it is not possible to blind participants to their treatment. This has led to the use of pragmatic RCTs where participants are randomised to receive an intervention or continue usual primary care.[11, 42] Such studies can be affected by disappointment bias, behaviour-modification bias, and differential drop-outs when those selected as controls had hoped to receive the intervention under investigation. Cohort multiple RCTs, as will be used in this study, have been adopted to prevent such biases.[43, 44] In this study design a cohort of people with the condition of interest are recruited (in this case the IMHW) and consented to be approached to complete further questionnaire surveys, for their GP medical records and prescriptions to be accessed and used as a comparator for future studies, and to be approached for participation in future studies if eligible. Clinical and patient-reported outcomes are captured at regular intervals, allowing those eligible for any given study to act as a control without being informed about the experimental intervention and thus minimising the bias associated with pragmatic trials.

ETHICS AND DISSEMINATION

This protocol was approved by the East Midlands-Derby Research Ethics Committee (18/EM/0288) and registered at clinicaltrials.gov (NCT03670706). The trial will be reported according to CONSORT guidance and standards.[45] The results will be submitted for publication in peer-reviewed academic journals. Any modification to the approved protocol will result in re-submission to gain approval from the REC and study sponsor.

LEGENDS

Figure 1 Participant timeline through the study

IMHW: Investigating Musculoskeletal Health and Wellbeing cohort study; GP: General Practitioner; OA: Osteoarthritis; RCT: randomised-controlled trial; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Figure 2 Analgesic sequence for pharmacological component

NSAID: Non-steroidal anti-inflammatory drug

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AUTHOR STATEMENT

MH, PN, BM, RO, AV, RN, MD, DAW and AA conceived the study. All authors contributed to the study design. MH, AF and AA wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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COMPETING INTEREST STATEMENTS

All authors declare no competing interests.

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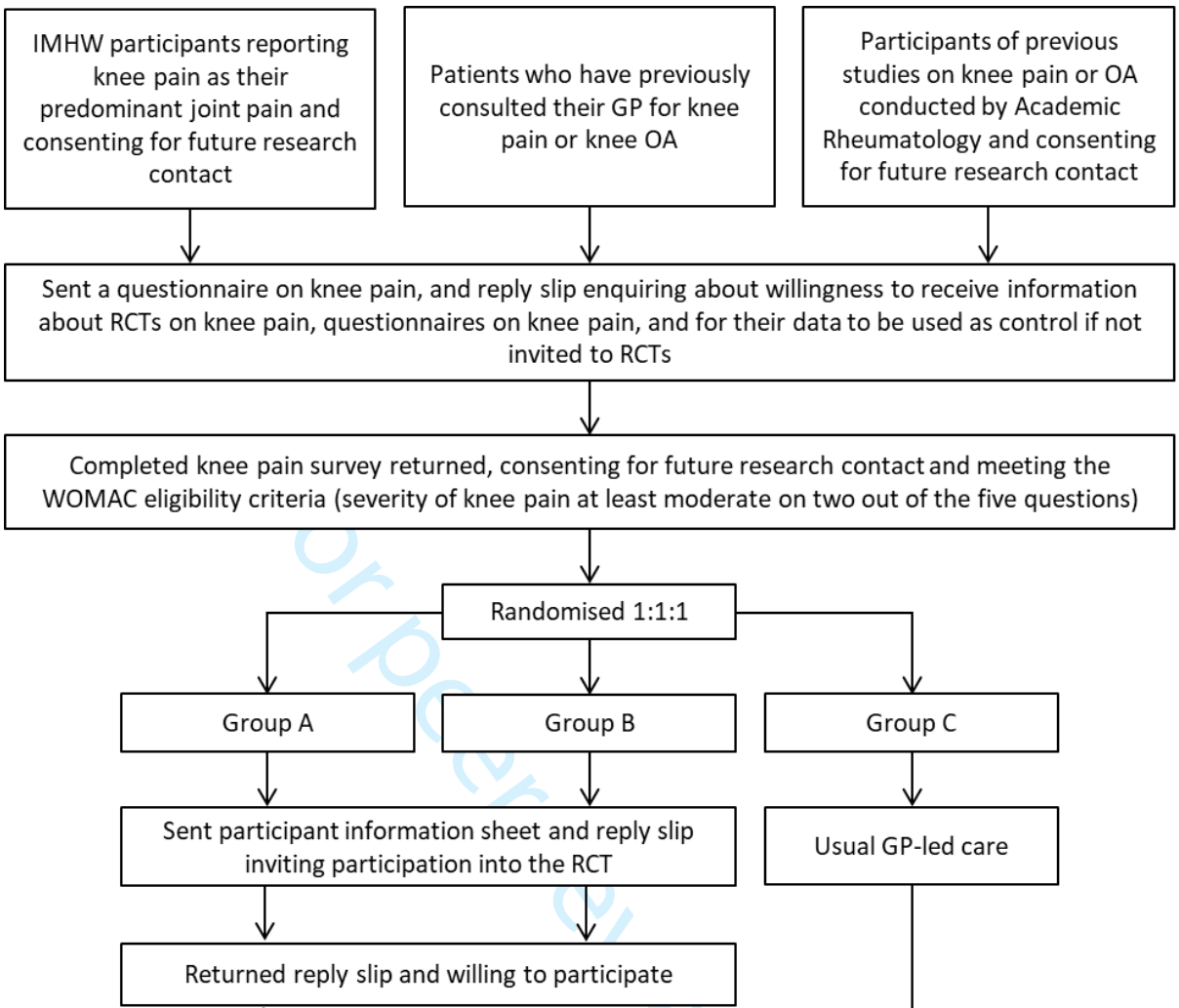

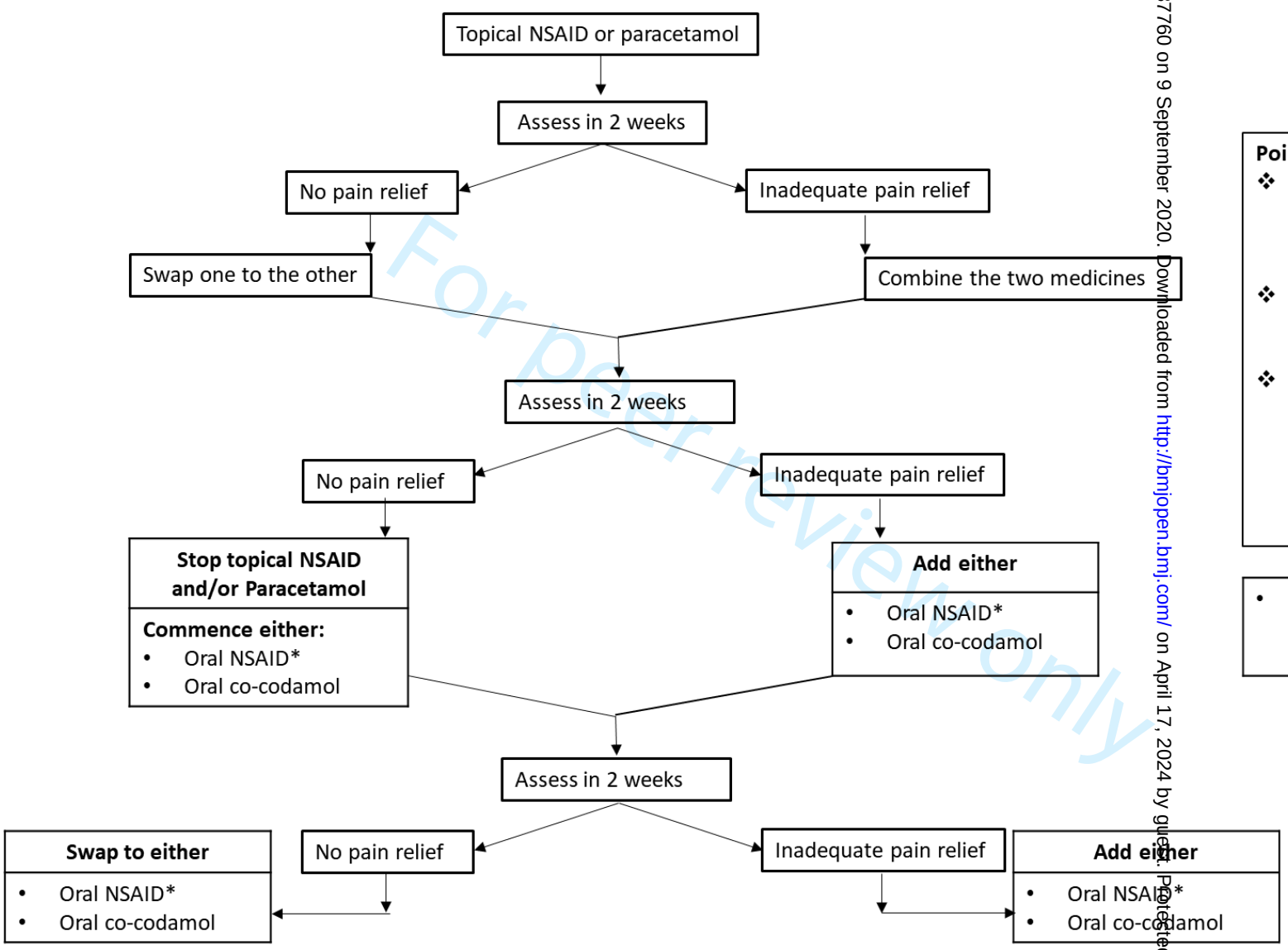

Points to consider:

- ❖ Do not combine topical and oral NSAID* if using oral NSAID stop topical NSAID
- ❖ If using 2 gels leave 3-4 hours gap between 2 applications
- ❖ Co-codamol contains paracetamol. So should not be combined with paracetamol. Stop Paracetamol if starting co-codamol

- Prescribe oral proton pump inhibitor with NSAID*

MUSCLE FUNCTION TESTING:

Isometric strength of the knee extensor muscles will be determined (best of 3 attempts) during a static maximal voluntary contraction. Peak power output and fatigue will be determined during 20 maximal isokinetic knee extensions at an angular velocity of 90°/s, which ensures all muscle fibres of the quadriceps muscle group are recruited [34]. All muscle function testing will be performed using an isokinetic dynamometer (HUMAC Norm, CSMi Solutions, MA, US).

QUANTITATIVE SENSORY TESTING (QST):

Pressure pain threshold (PPT)

PPT involves gently pressing on one place with a small handheld instrument called an algometer. A finger-width, soft rubber probe gently presses down and gradually increases pressure. The participant presses a button to stop the test as soon as the feeling of pressure become one of pain. The algometer is removed as soon as the button is pressed. The PPT measurements may be performed 3 times each at 3 different places:- on the forearm (brachioradialis muscle), knee (medial joint line, inside surface of the knee) and leg muscle (anterior tibialis). The pain from PPT should be mild, as we are asking only about the first feeling of pain. Each PPT lasts for less than 30 seconds. The participants will be familiarised with the test before it is administered so that they know what to expect and how we would like them to respond.

Temporal summation (TS)

TS involves a blunt metal wire with a small weight attached that has been built into a pen-shaped device, and this is applied to the skin. The feeling is one of sharpness, but the skin is not broken. The test is applied 5cm above the knee cap, on the skin at the bottom of the front of the thigh. The participant is stimulated once by the device and asked to rate their pain/discomfort from 0-10. They then have 10 applications in the same place, at a rate of 1 per second, and are asked to rate the average feeling. Two TS measurements will be done. A large majority of healthy participants and people with knee pain rate pain as less than 4/10 from TS, and each TS measurement lasts for less than 30 seconds. The given scores will be noted.

Conditioned Pain Modulation (CPM)

PPT will be measured on the proximal anterior tibialis. A manual blood pressure sphygmomanometer will be applied to the opposite upper limb, and inflate to above the systolic pressure. The participant will squeeze a ball in their hand and inform researcher once the pain or discomfort in the upper limb reaches 4/10. PPT will be measured at the proximal anterior tibialis anterior as described earlier.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	__21_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,_21_____
	5b	Name and contact information for the trial sponsor	___21_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___4_____
	6b	Explanation for choice of comparators	___5_____
Objectives	7	Specific objectives or hypotheses	___4,5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7, 8_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, 9,10,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	supplementary file _____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__9_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_ 11, 12, 13___

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Figure 2 Table 1 p10 Table 2 p12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__13 _____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____5, 6___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_11,12 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__7, 8, 13___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The East Midlands Knee Pain Multiple Randomised Controlled Trial Cohort Study: Cohort Establishment and Feasibility study protocol

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Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY

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The East Midlands Knee Pain Multiple Randomised Controlled Trial Cohort Study: Cohort Establishment and Feasibility study protocol

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ABSTRACT

Introduction: Knee pain due to osteoarthritis (OA) is a common cause of disability. The UK National Institute of Health and Care Excellence (NICE) OA guidelines recommend education, exercise and weight-loss advice (if overweight) as core interventions before pharmacological adjuncts. However, implementation of these in primary care is often suboptimal. This study aims to develop a complex intervention with non-pharmacological and pharmacological components that can be delivered by nurses. The feasibility and acceptability of the intervention, and feasibility of undertaking a future cohort-randomised controlled trial (RCT) will be explored.

Methods and analysis: In phase 1, we will develop a training programme for nurses and evaluate the fidelity and acceptability of the non-pharmacological element of the intervention. Fidelity checklists completed by the nurse will be compared to video-analysis of the treatment sessions. Patients and nurses will be interviewed to determine the acceptability of the intervention and explore challenges to intervention delivery. The non-pharmacological component will be modified based upon the findings. In phase 2, we will assess the feasibility of conducting a cohort RCT comprising of both the pharmacological and modified non-pharmacological components. We will compare three groups: group A will receive the non-pharmacological components delivered before pharmacological components; group B will receive pharmacological components followed by the non-pharmacological components; and group C (control arm) will continue to receive usual care. Study outcomes will be collected at 3 time points: baseline, weeks 13 and 26 after randomisation. Qualitative interviews will be conducted with a sample of participants from each of the two active intervention arms.

Ethics and dissemination: This protocol was approved by the East Midlands-Derby Research Ethics Committee (18/EM/0288) and registered at clinicaltrials.gov (NCT03670706, protocol v4.0, 10/02/2020). The study will be reported in accordance with the CONSORT guidance and standards. The results will be submitted for publication in peer-reviewed academic journals.

KEYWORDS

Feasibility, Complex intervention, Knee pain, Osteoarthritis, Nurse-led care, exercise, Weight-loss, Education, Analgesia

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to develop and evaluate the feasibility of a wholly nurse-led intervention following the core NICE guidelines for treating knee pain and OA.
- This study will not determine the effectiveness of this model of care for knee pain and OA, but will explore the feasibility of implementation and running an adequately powered randomised-controlled trial (RCT) and determine signal of efficacy.
- Assessing fidelity of intervention delivery will allow us to explore the extent to which the nurses can deliver individual components of the complex package of care as planned, and alongside exploring its acceptability will inform refinements to nurse training and/or the package of care.
- Blinded outcome assessment.
- Participants and nurses delivering care will not be blinded to each intervention. However, in utilising a cohort RCT study design where participants will be informed that their data may be used as a control comparison for intervention studies, bias associated with disappointment, behaviour-modification and drop-outs in the control arm will be minimised.

INTRODUCTION

Chronic knee pain affects one in four people aged 55 years or older, and is most commonly caused by osteoarthritis (OA).[1] The global prevalence of symptomatic knee OA is estimated at 4%, and it has an important impact on both affected individuals and health and social care systems.[2,3] The socio-economic and healthcare burden of knee OA is likely to increase due to the ageing population and the obesity epidemic.[2,4]

Best practice guidelines for managing OA published by the National Institute for Health and Care Excellence (NICE) recommend individualised patient education, advice and access to information about OA and its management, strengthening and aerobic exercise, and guidance on losing weight if applicable as core treatments, with consideration of adjunctive pharmacological and other non-pharmacological treatments as required.[5] However, core treatments are frequently under-utilised as both doctors and patients predominantly focus on pharmacological options including opioids.[6,7] Most people with OA feel they do not receive the treatment they need from general practitioners (GP), with an overemphasis on prescription drugs and lack of discussion about exercise and diet.[8] Given the growing concerns about the overuse of opioids for musculoskeletal pain including OA [9], it is important to explore alternative models of healthcare delivery with an emphasis on non-pharmacological interventions for this condition. Additionally, whilst it has been suggested that optimising analgesia prior to participation in exercise therapy may enhance adherence and patient outcomes, this has not been confirmed in a randomised controlled trial.[10]

Alternative models for implementing OA care have shown potential. The MOSAICS trial explored the effectiveness of delivering an enhanced initial consultation with GP and provision of nurse-led follow-ups as a clinically practicable way of implementing NICE guidelines compared to usual care.[11] However, only 29% of patients in the intervention arm reported having a consultation with a nurse, making it difficult to determine whether a nurse could help deliver the core NICE recommendations. Others have included using community physiotherapists and pharmacists for delivering interventions but have only demonstrated short-term improvements in health outcomes.[12]

The majority of patients with knee pain self-manage their symptoms, and those who seek healthcare, are managed by their GPs and community physiotherapists in the first instance.[8] A potential role for practice nurses has been identified [13] and nurse-led clinics already exist for patients with long-term conditions such as coronary heart disease,[14] heart failure,[15] and diabetes[16] resulting in equivalent or better outcomes for patients compared to usual GP-led care. Upskilling practice nurses to deliver the management of long-term conditions is recognised as a key strategy for the future of primary care.[17] This paper describes the protocol for developing and testing the feasibility of a wholly nurse-led intervention for people with knee pain, delivering the core NICE recommendations.

Further to this, it will test the feasibility of a cohort-randomised controlled trial. The usual double-blind placebo-controlled RCT cannot be utilised when investigating the efficacy of complex interventions for

knee pain as it is not possible to blind participants to their treatment. This has led to the use of pragmatic RCTs where participants are randomised to receive an intervention or continue usual primary care.[12,18] Such studies can be affected by disappointment bias, behaviour-modification bias, and differential drop-outs when those selected as controls had hoped to receive the intervention under investigation and drop out when allocated to the control arm. Cohort RCTs, as will be used in this study, have been adopted to prevent such biases.[19,20] In this study design, a cohort of people with the condition of interest are recruited and consented to be approached to complete further questionnaire surveys, for their GP medical records and prescriptions to be accessed, to be used as a comparator for future studies, and to be approached for participation in future studies if eligible.[21] Clinical and patient-reported outcomes are captured at regular intervals, allowing those eligible for any given study to act as a control without being informed about the experimental intervention and thus minimising the bias associated with pragmatic trials.

Aims and objectives

The overall purpose is to develop and test the feasibility of a nurse-led intervention for people with knee pain using a cohort-randomised controlled trial study design.

This study has two phases:
Phase 1 involves the development and evaluation of the non-pharmacological treatment component. Specific objectives of phase 1 are to: [1] develop a training package for nurses to deliver the core non-pharmacological and, pharmacological principles to manage knee OA as recommended by NICE; [2] determine the fidelity of delivery of the nurse-delivered components of the intervention; [3] explore patient and nurse acceptability of the non-pharmacological components of the intervention.
Phase 2 will test the feasibility of a cohort-randomised controlled trial of nurse-led versus usual care of people with knee pain and explore whether such a trial should provide analgesia before non-pharmacological interventions.

METHODS

Participants

Participants eligible for both phases of the study will be aged over 40 years and self-reporting knee pain on most days of the previous month for at-least three-months. Knee pain severity will be scored between 4-7 on a 0-10 numeric rating scale. This will be assessed using the following question “Over the past 4-weeks, how intense was the average pain or aching in your knees on a 0-10 scale, where 0 is no pain and 10 is pain as bad as could be?”

Exclusion criteria include participants who are unable to communicate in English, who are housebound or care home residents, on dialysis or home oxygen, pregnant or have dementia, serious mental illness, terminal cancer, autoimmune rheumatic diseases, asthma or lung disease requiring regular daily oral corticosteroids, unstable angina or heart failure, known peripheral vascular disease, stroke with residual weakness or sensory loss, physician-diagnosed peripheral neuropathy with

sensory or motor deficit, previous knee or hip replacement, on a waiting list for a knee or hip replacement or with severe knee pain (score >7 on NRS for average pain in past 4 weeks).

Nurses who undergo the intervention training and delivered the intervention in the study will be recruited to the qualitative components of the study and will give their consent to be interviewed in both phases of the study.

Recruitment

There are three routes of recruitment:

1. Participants will primarily be recruited from the Investigating Musculoskeletal Health and Wellbeing (IMHW) survey (NCT03696134), a cohort study that aims to measure and characterise the development and progression of pain, frailty and disability and form a longitudinal context for nested research.[21] Participants who self-report knee pain as their predominant body pain and consent for future research contact will be sent a questionnaire enquiring about their knee pain, mood, function and quality of life. They will also be asked about willingness to receive information about trials on knee pain, complete further questionnaires on knee pain, and for their data to be used for comparisons with other participant groups in research studies. Those willing and meeting the eligibility criteria will be invited to take part in the current study (Figure 1).
2. Additional participants identified by screening of GP records for previous consultation for knee pain will be sent a questionnaire as outlined above.
3. Finally, people with knee pain or OA who have taken part in previous community-based surveys in Academic Rheumatology, University of Nottingham and consented for future research contact may be approached with a questionnaire.

Setting

Study visits for research assessment will occur at Academic Rheumatology, City Hospital Nottingham, UK and the David Greenfield Unit, Queen's Medical Centre, Nottingham, UK. The intervention will be delivered at Academic Rheumatology, City Hospital Nottingham.

Consent and withdrawal

All participants will give written informed consent before entering the study and before any assessments or interventions related to the study are undertaken. Optional consent will be sought for video-recording of the intervention sessions to evaluate fidelity and audio-recording of participant interviews. Participants will be free to withdraw at any time if they desire to do so, or at the discretion of the chief investigator. In the event of withdrawal, any data collected up until that point will be kept and potentially included in any analyses.

Patient and Public Involvement (PPI)

The design of this study was supported by a patient advisory group of three people with hip or knee OA and a range of experiences in primary and secondary care. The group recognised the challenges of providing full explanations and individualised advice in a time-limited GP consultation and agreed that a wholly nurse-led intervention would be acceptable or preferable to most people. They provided input into the content of the both pharmacological and non-pharmacological components, the number and length of intervention sessions and the use of exercise diaries and educational content

PHASE 1: DEVELOPMENT OF THE NON-PHARMACOLOGICAL COMPONENT

The non-pharmacological intervention will be developed according to the Medical Research Council (MRC) framework for developing complex packages of care.[22] It was informed by several strands of evidence including current guidelines, an expert multi-disciplinary team of physiotherapists, rheumatologists and nurses, patient opinion, physiological considerations and behaviour change theory.

In brief, the intervention consists of a holistic assessment of the participant, individualised education about OA, aerobic and strengthening exercises and weight loss advice if required. Evidence-based strategies to motivate participants and support adherence to healthy behaviours will be employed.

The training package

A training package for nurses will be developed and piloted during this phase. Research nurses will be recruited without any prior knowledge of treating musculoskeletal conditions. The content will be based on current NICE guidelines for the management of OA [5] and a report by Arthritis Research UK on the educational needs of health professionals working with people with OA.[23] Academic and clinical experts and members of a PPI group have provided input into the training package.

Delivery of the training package will be underpinned by educational theory [24] and will build on the nurses existing knowledge of the condition. Training will be delivered in face-to-face sessions, complemented by a range of learning resources including a manual, case-studies, online resources and patient simulations. Key components of the training will include:

- The epidemiology and nature of knee pain and knee OA
- Assessment of the patient with knee OA
- Core NICE guidelines for managing OA
- Principles of strengthening and aerobic exercise prescription for knee OA
- Information and advice to support weight loss
- Strategies to support behaviour change
- Pharmacological management of OA and knee pain following a step-wise protocol of optimising analgesia

Study design

A pre-post intervention study using mixed quantitative and qualitative methods to determine the fidelity of delivery and the acceptability of the intervention by patients and nurses. After the nurse training, 20 participants with knee pain will be recruited to this study. They will receive the non-pharmacological components of the intervention covering as described above in four sessions over a five-week period.

Quantitative methods

Fidelity of delivery refers to the assessment of whether content of the sessions were delivered as intended. This will be assessed using a priori fidelity checklist of 5-8 categories and individual components (additional file 1). Categories included materials, introduction, assessment, education, exercise, weight loss, adjunct treatments, and review and planning. All interventions in this phase will be video-recorded (with consent). Nurses will self-complete the checklist after each session and a researcher will independently complete the checklist using the video recordings. The individual components of each category for each session will be rated as being complete, partially complete, not completed or not applicable. A sample of videos recordings will be reviewed by a second researcher to determine inter-rater reliability.

Quantitative analysis

Fidelity scores will be presented as the percentage of components that were delivered as intended for the overall delivery of the intervention, for each session and for each category. Inter-rater reliability between the two researchers scoring the video-recordings will be reported, as will the level of agreement between nurse-completed scores and researcher-completed (video) scores. For delivery of complex interventions such as this, levels of fidelity have been previously interpreted as 'high' fidelity where 80-100% of the specified components were delivered as intended, 'moderate' 51-79%, and 'low' 0-50%.[25] Where the fidelity scores are less than 80%, we will explore further to establish which components are responsible.

Qualitative methods

Acceptability of the intervention will be explored in a face-to-face interview with all participants who received the intervention. Participants who withdraw from the intervention will be offered the opportunity to take part in an interview to explore their experiences and reasons for discontinuation. The nurses who deliver the intervention will also be invited to interview, to explore their views on the training, experience in delivering the intervention, and perceived factors influencing the fidelity of delivery. Interviews will be carried out by a PhD student (PN) and overseen by two experienced qualitative researchers (AF and RN). All interviews will be audio recorded and transcribed verbatim by an external specialist company Transcribe It® and anonymised.

Qualitative analysis

After data transcription, all data will be checked for accuracy before transcripts are imported to NVivo 12. Qualitative data will be analysed using a Framework approach.[26] This method sits within the broad family of thematic analysis, but is particularly useful for research that has specific questions and a priori issues that need to be dealt with.[27] The analysis will follow the five stages of Framework analysis: familiarisation with the data, construction of an initial thematic framework, indexing and sorting the data using initial thematic framework, finalisation of thematic framework, summarising and displaying the data into a matrix. Emergent themes and subthemes will be discussed and agreed by at least two researchers to increase the validity of the analyses.

Following the fidelity evaluation and qualitative interviews, modifications may be made to study materials, procedures or protocol, and/or nurse training.

PHASE 2: FEASIBILITY COHORT RCT

Trial design

This will be a single centre, mixed-methods feasibility cohort RCT. Participants will be recruited as described above and randomised to one of 3 treatment arms (figure 1).

Group A will receive the non-pharmacological protocol for 13 weeks followed by the pharmacological protocol between weeks 13 and 26 as required,
Group B will receive the pharmacological protocol in the first 13 weeks followed by the non-pharmacologic protocol between weeks 13 and 26 with optimised background analgesia.
Group C is a control (cohort) group and will continue to receive usual care.

Randomisation and allocation concealment

Participants will be individually randomised on a 5:5:1 ratio using randomly permuted block sizes of 3 and 6, stratified for the number of eligible knees (i.e. unilateral or bilateral knee pain). Randomisation codes will be generated by the study statistician. Allocations to groups will be enclosed in serially numbered, opaque, sealed envelopes with a carbon copy paper. The serially numbered opaque envelopes will be packaged and prepared by an independent member not belonging to the research team. Participants will be randomised by the trial coordinator who will ensure that the envelopes are opened sequentially, and only after the participant's unique study identifier are written on the outside of the appropriate envelope.

Blinding

It is not possible to blind the study participants or the nurse delivering the intervention to the group allocations. However, study personnel involved in outcome assessment and data analysis will be blinded. Participants will be requested not to disclose group allocation to the outcome assessor, but if this does occur it will be recorded. Only once data has been cleaned and analysed will the treatment allocation be made known.

INTERVENTION

The intervention will be delivered by the same nurse as in phase 1, any additional nurses recruited will undergo the same training.

Non-pharmacological component

The non-pharmacological component will be delivered by a nurse as detailed in table 1 incorporating any modifications made following the development phase (a detailed description is included in additional file 2). It will be delivered in up to six face to face sessions over 13 weeks. Participants will continue their usual analgesics in this period.

Table 1 Content of non-pharmacological component of intervention

Content of non-pharmacological component	Session					
	1	2	3	4	5	6
Assessment						
Holistic assessment including symptoms, pain elsewhere, co-morbidities, impact on function, occupation, mood, sleep, illness perceptions, current levels of PA, and attitudes to PA and weight loss (if required)	✓					
Physical assessment of knee range of movement, lower limb muscle strength, observation of gait and functional activities, BMI.	✓					
Education & Advice						
Provision of ArthritisResearchUK booklet "Osteoarthritis of the knee"	✓					
Nature of Osteoarthritis	✓					
Adverse illness perceptions addressed	✓					
Core treatments	✓					
Benefits of exercise and PA	✓					
Pacing	✓					
Benefits of weight loss (if required)	✓					
Use of heat and cold for pain,	✓					
Appropriate footwear, use of walking aids	✓					
Signposting to further information if required	✓					
Review of above if required		✓	✓	✓	✓	✓
Exercise (individualised programme)						
Strengthening exercise	✓					
Aerobic exercise/ PA	✓					
Functional exercises	✓					
Stretching exercises	✓					
Review performance of exercise		✓	✓	✓	✓	✓
Progression/regression of exercises		✓	✓	✓	✓	✓
Weight loss (if required)						
Previous efforts to lose weight discussed	✓					
Strategies for weight loss discussed	✓					
Agree weight loss goal (5% body weight)	✓					
Signposting to resources (weight loss groups, NHS weight-loss plan)	✓					
Review of weight-loss progress and advice		✓	✓	✓	✓	✓
Adherence/behaviour change strategies						
Patient goals and action plan recorded for exercise and weight loss	✓	✓	✓	✓	✓	✓
Patient's confidence to achieve goals discussed and recorded	✓	✓	✓	✓	✓	✓
Barriers and facilitators discussed	✓	✓	✓	✓	✓	✓
Exercise diary completed and discussed	✓	✓	✓	✓	✓	✓

PA, Physical activity; BMI, Body Mass index.

Pharmacological component

The nurse will take a history of current symptoms, co-morbidities, medications and the main knee complaint of the participant. They will be advised by the nurse to continue on their current analgesia prescribed by their GP, and to add in simpler and safer analgesics in the sequence shown in figure 2. Once they are on a simpler and safer analgesic, they will be advised to reduce the dose of potentially more toxic or stronger analgesic. However, this will depend on the subjective improvement the participant experiences with simpler analgesic.

Relative and absolute contra-indications will be assessed against a checklist developed from the British National Formulary (BNF). Participants with absolute contraindication to an analgesic will not be prescribed that drug. Participants with relative contraindications may be prescribed the aforementioned drug if they are willing to do so after exploring risks and benefits.

Analgesics will be reviewed at two-weekly intervals over a 13-week period and optimised if the pain relief is insufficient. This will be done over the phone, or at a face-to-face visit, depending on participant preference. The visits and telephone consultations will be conducted by the nurse and prescriptions signed by the principal investigator or nominated deputy. Once a participant achieves adequate pain control and does not request any further changes to their analgesia, they will be advised to contact the nurse by phone for changes to their treatment if needed during the study.

Usual care

Participants allocated to this group will continue to receive usual care for their knee pain. They will not undertake any of the clinical assessments and will not receive any input from the nurse. People in this group will be part of the baseline cohort and will not be aware of the content of the invention groups.

Concomitant treatments

Participation in the trial does not preclude the participants from receiving any concomitant care or treatment.

Quantitative Study Outcomes

The feasibility of running a full trial will be assessed by recording the following data:

- Recruitment rates
- Dropout rate and reasons for drop-out
- Number of scheduled nurse appointments attended
- Number of instances of unblinding
- Completeness of questionnaire data
- Concordance with exercise assessed using data from participants' exercise diaries (total number of days on which exercises were performed)

Participant-reported measures

A summary of all participant outcomes to be collected at 0, 13 and 26 weeks for groups A and B are presented in table 2 and in additional file 3.

Table 2 Summary of questionnaire and research measures to be collected

Domain	Data Source	Measure / Instrument	Time points (week)
Demographic characteristics	Research assessment	Age, height, weight	0 0,13,26
Comorbidities & medications	Research assessment	Comorbidities, current medications	0 0,13,26
Radiographic evaluation	Research assessment	Bilateral knee radiographs: PA semi-flexed weight-bearing and skyline views [28] scored for Kellgren and Lawrence grades and using the Nottingham line drawing atlas [29]	0
Knee Pain	Self-report	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [30]	0,13,26
	Self-report	Analgesic and NSAID consumption	0,13,26
	Research assessment	Quantitative sensory testing† including pressure pain detection threshold, temporal summation and conditioned pain modulation	0,13,26
Physical Activity	Self-report	International Physical Activity Questionnaire (IPAQ) [31]	0,13,26
Function	Self-report	WOMAC function subscale [30]	0,13,26
	Research assessment	Timed Up and Go (TUG) test [32] 30-second chair stand test [33]	0,13,26
Muscle Function	Research assessment	Isometric and isokinetic quadriceps strength†	0,13,26
Quality of life	Self-report	The Short Form (36) Health Survey V2 [34] EQ-5D-5L™ [35]	0,13,26
Psychological wellness	Self-report	Hospital Anxiety and Depression Scale (HADS) [36]	0,13,26
Healthcare use	Self-report	Service use questionnaire to assess use of NHS or private healthcare, prescription and over-the-counter medicines related to knee pain outside of the study	0,13,26
Participant engagement in treatment	Nurse completed questionnaire	Pittsburgh Rehabilitation Participation Scale(PRPS) [37]	13/26*
Exercise adherence	Self-report	Adherence to Exercise Scale for Older Patients (AESOP) [38]	13/26**
Acceptability of intervention	Self-report	Participant satisfaction with treatment	13,26
Blood markers	Research assessment	Non-fasting serum cholesterol, HbA1c and C-reactive protein ††	0,13,26
Safety	Case Report Form	Adverse events	26

* This will be completed by the nurse after each of the non-pharmacological sessions.

** This will be completed by the participant at the end of non-pharmacological arm.

† further description included in detailed in the additional file 3 and †† file 4.

Group C will receive a questionnaire at week 26, enquiring about healthcare utilisation, demographic characteristics, self-reported height, self-reported weight, current alcohol intake and smoking status, comorbidities, medications, joint pain, central aspects of pain in knee scale, WOMAC, SF-36v2, and HADS.

Safety and adverse events (AEs)

This study intervention follows current NICE guidelines that might offered as part of routine clinical care. As such the risk of severe or unexpected adverse events in low.[39] Exercise and an increase in physical activity may initially increase the risk of adverse events such as pain, fatigue or muscle soreness or increased falls through increased activity. To reduce the risk of adverse events the exercise programme will be tailored to the abilities of the participants. All AE serious and non-serious will be monitored and recorded through the study by the nurses and will be managed in line with current NIHR guidelines.[40]

Qualitative Study Outcomes

Acceptability of the intervention will be assessed using qualitative interviews conducted after the intervention (week 26) with approximately 10 participants from each of the intervention arms (Group A and B). They will be purposively selected to represent those with likely low- and high-concordance with the exercise advice using the AESOP questionnaire. Interviews will explore participants' overall satisfaction with the intervention and the sequence of treatment, perceptions of nurse-led care and previous treatment experience, level of adherence to the advice, perceptions of managing their knee pain, as well as perceived impact of their knee pain on their daily life before and after the intervention. Participants who withdraw from the intervention will be offered the opportunity to take part in an interview. Interviews will also be conducted with the study nurses to explore their experience in delivering the intervention, perceived effectiveness of the intervention and barriers to implementation and how these may be overcome.

Sample size

Quantitative study

As this is a feasibility study, a formal sample size calculation for between group comparisons of primary clinical outcome is not appropriate. A target sample size of 53 participants per arm will be sought over the recruitment period to reliably estimate the feasibility outcomes relating to recruitment and retention rates to inform a fully powered RCT. With a sample size of 159 (53 participants per arm), we will be able to estimate a drop-out rate of no more than 20% to within 7% points of the true value with 95% confidence.

Qualitative study

Target recruitment will be 20 participants, ten from each intervention arm. However, final numbers will be determined by data saturation, where no new themes are identified.

Data analysis

Feasibility outcomes will be estimated using descriptive statistics (with 95% confidence intervals) and will be presented overall and per randomised groups. A CONSORT diagram will summarise the flow of participants through the study. Reasons for non-eligibility, withdrawals and non-completion of follow-up questionnaires will be presented if available. As this is a feasibility study, interim analyses are not planned. Similarly, missing data will not be imputed, on the contrary, the pattern of missing data will be assessed. Protocol non-adherence will be assessed as randomised.

Quantitative analysis

The main quantitative analysis will be of the trial feasibility outcomes:

- Recruitment rate (per month, per recruitment source, per 100 participants approached)
- Dropout rate (per arm, per stage pharmacological/non-pharmacological)
- Attendance rates for scheduled nurse appointments
- Missing data
- Power and sample size calculation for a definitive trial will be based on WOMAC summated knee pain domain scores in the most painful knee at week 26.

Descriptive statistics will be presented for demographic data and all baseline clinical outcome measures. Exploratory analysis of clinical outcomes will be conducted according to randomised groups but will not be interpreted in terms of effectiveness. The emphasis will be on confidence intervals of effect size estimations rather than the p-values. Changes in clinical and patient-reported outcomes from baseline to 13 and 26 weeks will be analysed using appropriate parametric or non-parametric statistics. A comparison of those receiving the pharmacological component first with those receiving the non-pharmacological component first will help determine the order of delivery in a future trial.

Qualitative analysis

Interview data will be analysed following the framework approach as described in phase 1 [41]. Analysis will be conducted in parallel with the interviews and initial results will inform subsequent sampling and areas of interest to follow-up.

CRITERIA FOR TERMINATING THE STUDY

The study may be stopped by the sponsor if there is apparent futility in continuing with it.

DATA MANAGEMENT

Study data will be managed by the study co-ordinator (BM) under the supervision of the chief investigator (AA) and the study statistician (RO). A data monitoring committee has not been convened by the sponsor as this is a feasibility study using well established and NICE approved interventions. All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy

and informed consent, and will adhere to the Data Protection Act 2018 and the General Data Protection Regulation (EU) 2016/679 (GDPR). The Study Coordinator shall carry out monitoring of trial data as an ongoing activity. Trial data and evidence of monitoring and systems audits will be made available for inspection as required by the sponsor and the REC.

Qualitative data and video or audio recordings will be archived in the University of Nottingham servers using password protection. Quantitative trial data will be stored in REDCap database with range checks for data values. All quantitative data will be source data verified. 10% of the entered trial data will be audited and variables for which there is >5% error will be entered again. Once auditing is complete the electronic Case Report forms will be signed off and the database placed under hard lock. Study data will be available to the study statistician, PhD student and research fellow working on the project.

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required.

ROLE OF SPONSOR AND FUNDERS

There is no role of the study sponsors and funders in the design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The study sponsor and funder will have no ultimate authority over any of these activities.

ETHICS AND DISSEMINATION

This protocol was given approval approved by the East Midlands-Derby Research Ethics Committee (REC) (18/EM/0288) prior to commencing recruitment in November 2018 which is ongoing. The study was registered at clinicaltrials.gov (NCT03670706). The trial will be reported according to CONSORT guidance and standards.[42] The results will be submitted for publication in peer-reviewed academic journals. Any modification to the approved protocol will result in re-submission to gain approval from the REC and study sponsor. Authorship eligibility guidelines will be adhered to, and we do not intend to use professional writers. Any interested researcher will be able to access the full protocol, participant-level dataset, and statistical code for research purposes after data sharing agreement has been signed.

DISCUSSION

People with knee OA continue to often receive suboptimal fragmented care and the core NICE recommendations are under-utilised in primary care.[43] Given that knee pain is common, and there is a huge time-pressure on GPs in the UK, it is vital to find out if a complex package of care incorporating the core recommendations can be delivered by other healthcare professionals such as practice nurses.

We believe that a wholly nurse-led management programme where a nurse acts as the point of contact for people with knee pain due to OA, educates them about the condition, provides core pharmacologic and non-pharmacologic treatments, and builds a long-term therapeutic relationship is likely to be clinically effective and cost-effective in improving quality of OA care as demonstrated for other chronic conditions.[16,44-47]

This study will not provide an answer as to the effectiveness of a wholly nurse-led intervention for OA and knee pain, but will determine the feasibility of implementing this model of care and of testing it in a full trial using practice nurses. Assessing fidelity will play an important part in the development and evaluation of the intervention, by exploring the extent to which the nurses can deliver individual components of the complex package of care for knee pain as planned. Combined with qualitative interviews to explore their acceptability, this will provide insight into the suitability of the training and intervention to inform appropriate refinements to the whole package of care that can be tested in a full trial. Although the intervention will take place in a research setting rather than primary care, the study outcomes will provide insight into the feasibility of implementation into real-world practice.

Further, this study will explore at what point analgesia should be optimised within this complex package of care. Having two intervention groups, one where analgesia is provided before the non-pharmacological component and one where it is provided after, will help us determine whether patients exercise better when analgesia is optimised first, or whether they are able to exercise sufficiently before this. This will inform the order of treatment in a two-arm full trial.

LEGENDS

Figure 1 Participant timeline through the study

IMHW: Investigating Musculoskeletal Health and Wellbeing cohort study; GP: General Practitioner; OA: Osteoarthritis; RCT: randomised-controlled trial; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Figure 2 Analgesic sequence for pharmacological component

NSAID: Non-steroidal anti-inflammatory drug

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AUTHOR STATEMENT

MH, PN, BM, RO, AV, PG, RN, MD, DAW and AA conceived the study. All authors contributed to the study design. MH, AF and AA wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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COMPETING INTEREST STATEMENTS

All authors declare no competing interests.

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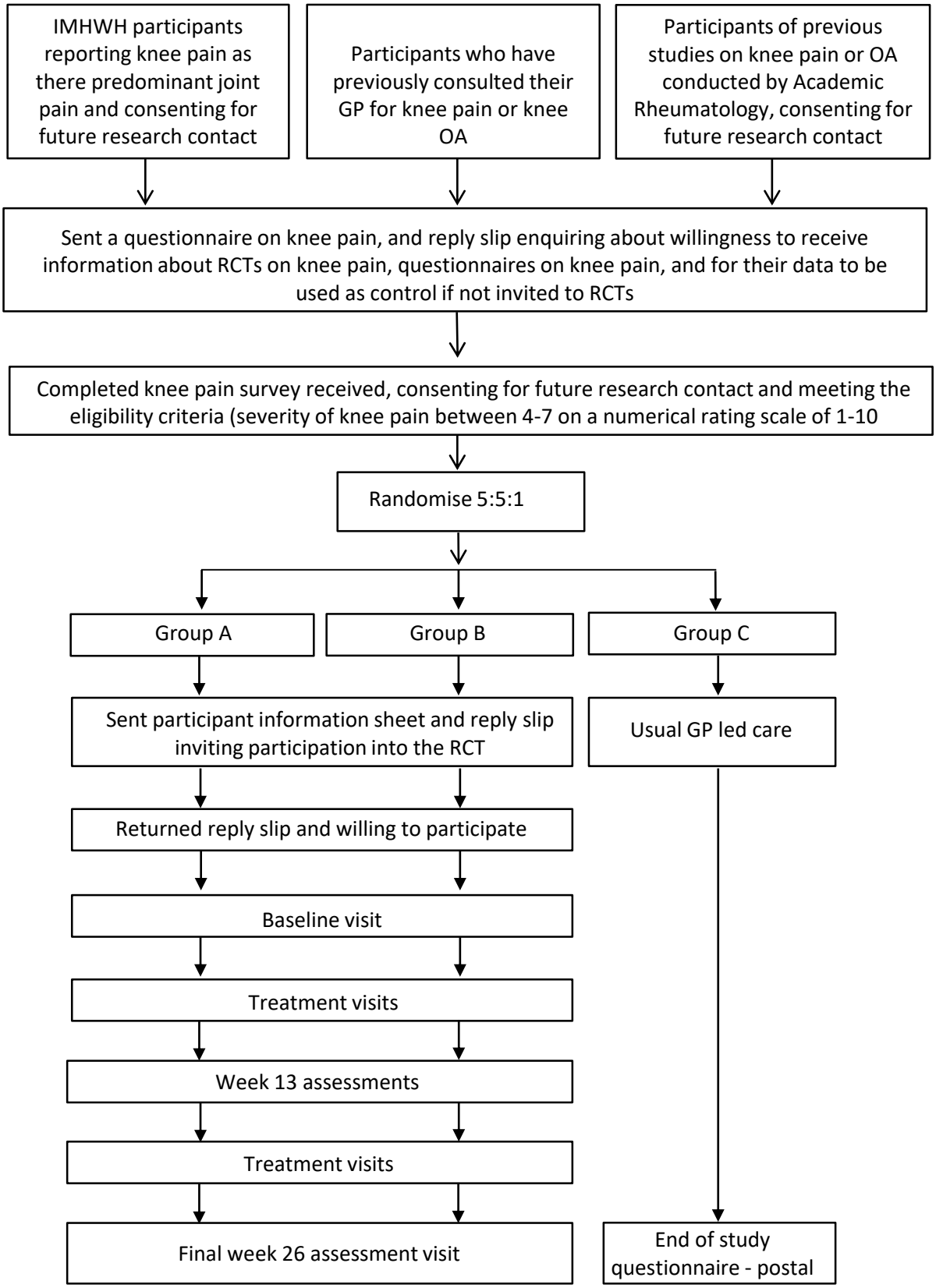
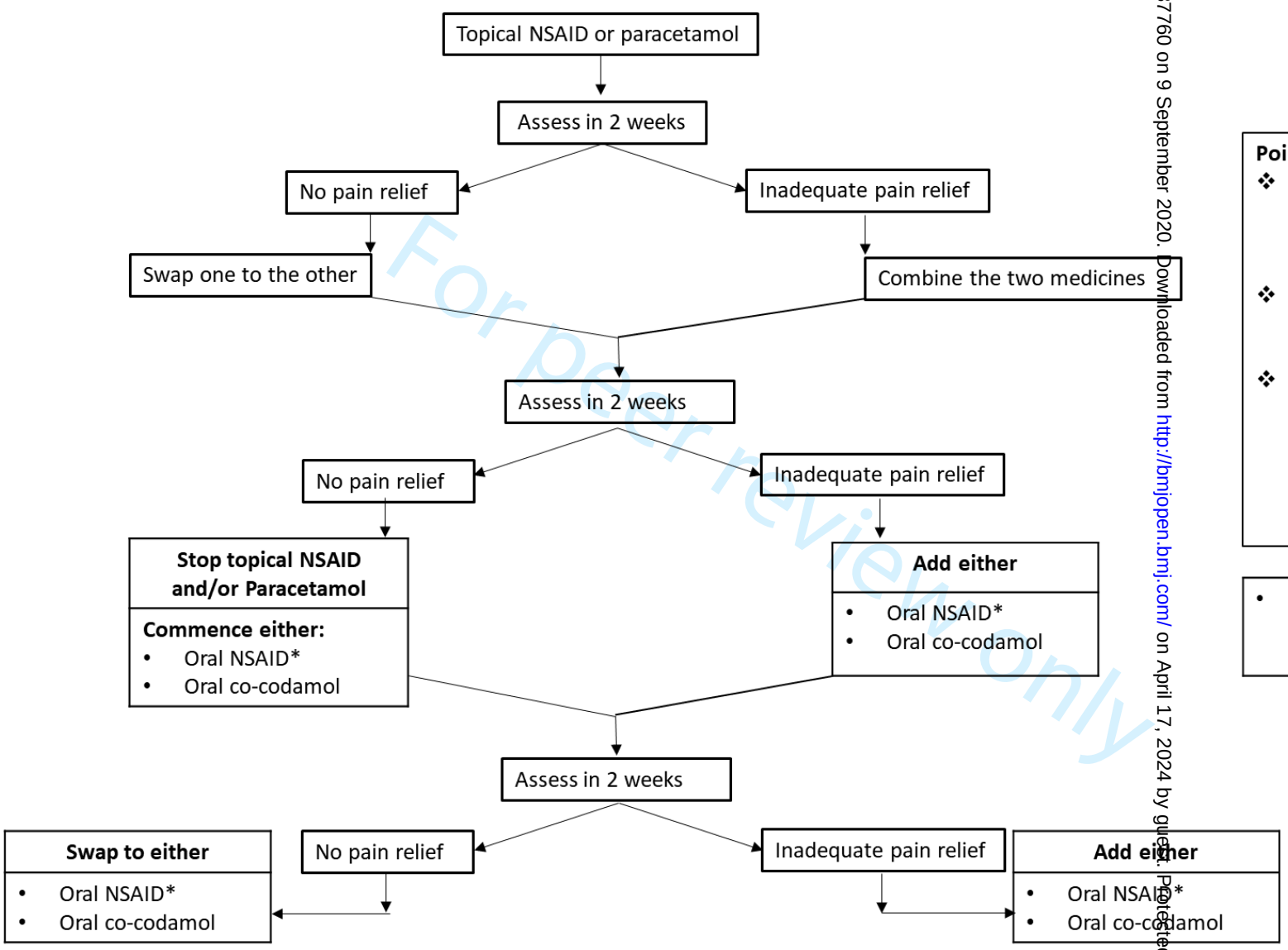
WORD COUNT

4557(excludes the title page, abstract, tables, acknowledgements, contributions and references)


IMHWH participants reporting knee pain as there predominant joint pain and consenting for future research contact
Participants who have previously consulted their GP for knee pain or knee OA
Participants of previous studies on knee pain or OA conducted by Academic Rheumatology, consenting for future research contact
Sent a questionnaire on knee pain, and reply slip enquiring about willingness to receive information about RCTs on knee pain, questionnaires on knee pain, and for their data to be used as control if not invited to RCTs
Completed knee pain survey received, consenting for future research contact and meeting the eligibility criteria (severity of knee pain between 4-7 on a numerical rating scale of 1-10
Randomise 5:5:1
Group A
Group B
Group C
Sent participant information sheet and reply slip inviting participation into the RCT
Usual GP led care
Returned reply slip and willing to participate
Baseline visit
Treatment visits
Week 13 assessments
Treatment visits
Final week 26 assessment visit
End of study questionnaire - postal



Points to consider:

- ❖ Do not combine topical and oral NSAID* if using oral NSAID stop topical NSAID
- ❖ If using 2 gels leave 3-4 hours gap between 2 applications
- ❖ Co-codamol contains paracetamol. So should not be combined with paracetamol. Stop Paracetamol if starting co-codamol

- Prescribe oral proton pump inhibitor with NSAID*

Additional File 1:
Quantitative Fidelity Checklist for non-pharmacological component of intervention

Session 1: **Intervention categories** **Individual components**	Complete	Not completed	Partially completed	Not applicable
Materials				
ARUK booklet on OA				
Exercise/activity diary				
Goal Setting forms				
Introduction				
Introductions				
Aim of interventions				
Content				
Structure				
Holistic assessment of person with OA.				
Illness perception of OA explored				
Pain severity explored				
Pain impact on occupation or social activity explored				
Current level of physical activity/ exercise and its intensity explored				
Views and attitudes to weight loss explored (if required)				
Issues with mood explored				
Sleep quality explored				
Support network and caregiver involvement discussed				
Co-morbidities				
Other MSK pain				
Inspection of knee				
Palpation of knee				
Active ROM				
Passive ROM				
Observation of Gait				
Education				
Illness perception of OA addressed				
Nature of OA discussed				
Core treatments for OA addressed				
Rationale for self-management strategies addressed				
Physical Activity /benefits of exercise addressed				
Activity rest cycle/pacing explained				
Reflection on activity/pacing and recommendations discussed				
Participants had the chance to contribute to discussion				
Exercise				
Warm up exercises explained/demonstrated				
Aerobic exercises explained/demonstrated				
Strengthening explained/demonstrated				
Stretching exercises explained/demonstrated				
Participants had the chance to practice prescribed exercises				
Exercise corrected if required				
Smart goals setting				
Action planning to carry out exercise				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators identified (if confidence low)				
Weight loss (if required)				
Previous efforts to lose weight discussed				
Healthy BMI range and weight loss discussed				

Additional File 1:
Quantitative Fidelity Checklist for non-pharmacological component of intervention

5% weight loss goal calculated with timescale				
Agree weight loss goal				
Action plan for weight loss				
Discuss strategies for weight loss (calorie deficit, portion size, meal planning, tops tips, slimming groups, increasing PA etc)				
Signpost to NHS weight loss plan				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Adjunct treatments				
Use of heat/cold discussed				
Walking aids discussed				
Footwear discussed				
Review and planning				
Session review: goal setting synopsis and action plan				

Complete = component was fully delivered by the nurse
Not Complete = component was not delivered by the nurse
Partially completed = there was an attempt to deliver this component by the nurse but it was not delivered fully
Not applicable = component was not applicable for example weight loss components if the participant had a body mass index < 25

Fidelity scores will be calculated for each category and each session as the percentage of completed components from the total number of components. Components which were not applicable will be excluded from the overall total.

Additional File 1:
Quantitative Fidelity Checklist for non-pharmacological component of intervention

Follow up session 2, 3: **Intervention categories Individual components**	Complete	Not Completed	Partially completed	Not applicable
Assessment				
Pain symptoms since previous visit explored				
Factors influencing pain explored				
Physical activity's levels explored				
Education				
Activity rest cycle/pacing explained				
Individual reflection on activity-rest cycle/pacing facilitated				
Physical activity's levels addressed				
Participants had the chance to contribute to discussion				
Exercise				
Exercise goals and action plan reviewed				
Exercise/activity diary reviewed				
Problem solving of previous weeks action plan				
Previous session exercises reviewed and performed by the participant				
Exercise corrected if required				
Smart goals reviewed				
Strengthening exercises progressed or adapted				
Aerobic exercises progressed or adapted				
Participants had the chance to practice strengthening exercises				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators carrying out the exercise identified(if confidence low)				
Weight loss (if required)				
Weight loss goal and action plan reviewed				
Weight reviewed				
Action plan updated				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Adjunct treatments				
Use of heat/cold discussed				
Walking aids discussed				
Footwear discussed				
Review and planning				
Session review: goal setting synopsis and action plan				

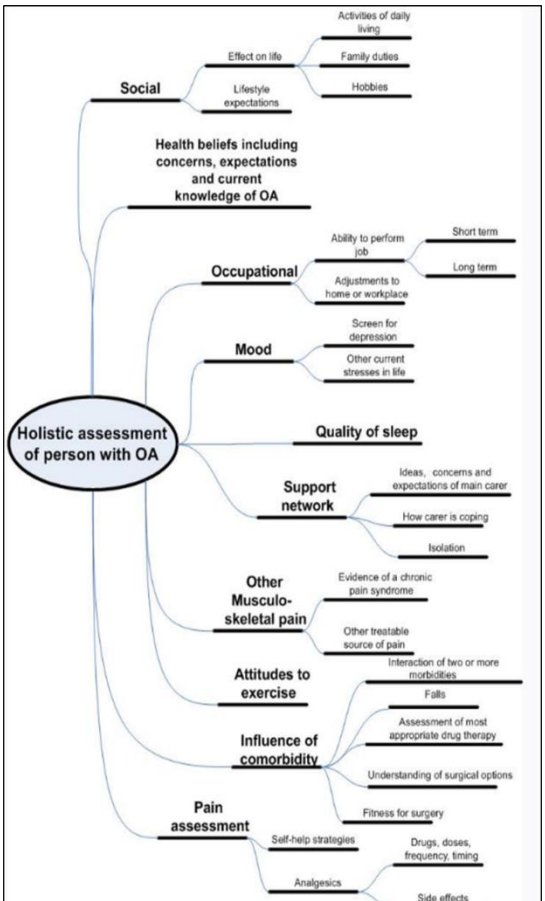
Additional File 1:
Quantitative Fidelity Checklist for non-pharmacological component of intervention

Final session: **Intervention categories** **Individual components**	Complete	Not completed	Partially completed	Not applicable
Assessment				
Pain symptoms since previous visit explored				
Factors influencing pain explored				
Physical activity's levels explored				
Education				
Long-term self-management addressed				
Participants had the chance to contribute to discussion				
Exercise				
Exercise goals and action plan reviewed				
Exercise/activity diary reviewed				
Problem solving of previous weeks action plan				
Participants had the chance to attempt and practice previous exercises				
Exercise corrected if required				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators carrying out the exercise identified (if confidence low)				
Exercises aiming for long term management given				
Weight loss (if required)				
Weight loss goal and action plan reviewed				
Weight reviewed				
Action plan updated				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Long term action plan for weight loss given				
Review and planning				
Session review – long term goal setting and action planning recap				

Additional File 2: Non-pharmacological intervention

The non-pharmacological component of the intervention consists of a holistic assessment of participant and the delivery of core treatments including patient information, exercise and weight loss (if required). The figure below will the nurses as to what issues could be included in the holistic assessment as recommended by NICE. Nurses will explore the impact of their knee pain on their day to day lives as well as their understanding of Osteoarthritis ,health beliefs around the condition and attitudes to exercise and weight loss (where required). The nurse will also carry out a simple knee examination observing any deformities, palpating for swelling, testing available range of movement, muscle strength of the knee and hip extensors and observation of gait and simple functional activities (sit to stand and stepping up and down).

Figure: Holistic approach to osteoarthritis assessment and management https://www.nice.org.uk/guidance/cg177



Patient Advice and information

The information and guidance contained within the Arthritis Research UK booklet *Osteoarthritis of the Knee* will be used as starting point for talking to patients about what they can do themselves to help with their knee symptoms. Misconceptions about OA will be addressed and a positive message about the benefits of exercise and maintaining a healthy weight will be promoted.

Advice on pacing, use of hot and cold for pain relief, wearing supportive and cushioned footwear and the use of walking will also be explored and participants sign-posted to other sources of information.

Additional File 2: Non-pharmacological intervention

Exercise

Both aerobic exercise and strengthening exercises will be prescribed for participants.

Aerobic exercise

Advice on aerobic exercise will be in line with current UK guidelines for physical activity (PA) that adults should aim to be actively daily and over a week activity should add up to at least 150 minutes of moderate intensity exercise. https://www.nhs.uk/live-well/exercise/physical-activity-guidelines-older-adults/ Moderate intensity exercise will be described to participants as activity that will cause them to get warmer and breathe harder and their hearts to beat faster. Participants current PA will be estimated by asking two simple questions:

- On how many days of the week do you carry out moderate (like a brisk walk) or greater physical activity?
- On those days how many minutes do you engage in this activity at this level?

Participants will be encouraged to identify when and where they could increase their physical activity and a goal will be with the participants to increase this.

Strengthening exercise

Participants will be given an individualised from a range of simple strengthening exercises, functional exercise and stretches (see Table 1). Initial prescription of strengthening and functional exercises will be set at 2 sets of 12 repetitions and increased or decreased according to rate of perceived exertion (RPE) on a 0-10 scale. Participants will be told they should feel like they were working hard (RPE 5-6/10) to complete 12 repetitions of a strengthening exercise. If the exercise is too hard ie <12 repetitions the nurse will reduce the load or change the exercise. If the exercise is too easy then the load will be increased (using theraband where appropriate) or a more challenging exercise set. Stretches will be given and held for 30 seconds and repeated 3 times. Warm-up exercises, strengthening and functional exercises, and stretches for the main lower limb muscle groups may be included as below. Individual exercise booklets will be provided in using PhysioTools software.

Weight Loss

After calculating participants Body Mass Index Participants who were overweight or obese will be given provided with evidence-based advice and guidance on losing weight. Beliefs about eating, physical activity and weight and their knee pain will be explored and any previous experiences of losing weight discussed.

Key advice for participants will be to focus on a calorie restricted diet with a reduction of fat and increase in dietary fibre. The NHS BMI calculator will be used to determine how much weight someone would need to lose to have a healthy BMI and estimate how long it might take (based on a 500 calorie reduction per day). https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/

Participants will be signposted to NHS weight loss plan which is a free 12 week diet plan with useful resources but will be free to use any method they prefer eg a commercial weight loss plan/group or other online weight loss apps. https://www.nhs.uk/Livewell/loseweight/Pages/Loseweighthome.aspx

An initial weight loss of goal of 5% will be suggested for participants as an initial goal, then increased to 10% if that was achieved in the study duration or until a healthy BMI was achieved.

Additional advice on eating regularly, portion sizes, reading food labels, alcohol and sugary drink consumption and meal planning will be provided.

Additional File 2: Non-pharmacological intervention

Table 1 Exercise programme

Warm-up exercises/Dynamic stretches	Simple movements to warm the body up and prepare for the exercises to follow • Marching on the spot (increase knee height from low, middle, high) • Rocking from heels onto toes • Knee slides (long sitting/lying)	
Strengthening exercises	Quadriceps	Static Quads contractions (sitting)
		Inner range quads
		Straight leg raises
		Leg press in long sitting with theraband
		Knee extension with theraband (sitting)
	Gluteals	Static glut contractions (prone lying)
		Hip extension in lying (knee bent)
		Hip abduction in side lying, knee bent (clam shell)
		Hip extension in lying (knee straight) +/- theraband
		Hip abduction in lying (knee straight) +/- theraband
	Hamstrings	Static Hamstrings contractions (sitting)
		Knee curls (in standing)
Functional exercises		Sit to Stand +/- theraband
		Mini Squats +/- theraband
		Partial wall squats
		Bridging
		Step-Ups (front/side)
		Step-Downs
Stretches		Quadriceps (lying or standing)
		Hamstrings (seated or standing)
		Calf muscle in standing at wall

Additional File 2: Non-pharmacological intervention

Motivation and behavioural change strategies

As well as providing participants with education about their condition and addressing negative illness perceptions, there are a number of strategies that will be used to motivate participants and support adherence to the intervention. These include:

1. **Establishing participants preferences for exercise and weight loss**
   These will be established during discussions with nurse and integrated into goals and actions planes.
2. **SMART goal setting**
   SMART goals are Specific, Measurable, Achievable, Relevant and Timely. These will be set in collaboration with the participant and nurse and will included physical activity/ exercise goals and weight loss goals if appropriate. A goal sheet will be completed with the participants and a review date set.
3. **Establishing self-efficacy (confidence) to achieve goals**
   Participant's confidence to achieve their goals will be assessed on a 10 point scale, where 0 represents no confidence and 10 extremely confident. Where confidence is <7/10 the nurse will explore reasons for this and looked at barriers and facilitators which might improve this.
4. **Identifying barriers and facilitators to achieve goals**
   Reasons for a lack of confidence will be explored by the nurse and potential solution discussed for example asking friends or family for support to engage in exercise or change eating habits
5. **Action planning and use of exercise diaries**
   Participant will have a written action plan of how, when and where they are going to undertake physical activity, carry out their exercise programme and make change to their diet. Adherence will be further supported by the use of exercise diaries so participants can self-monitor activities and bring to follow-up sessions to discuss with the nurse.

Follow-up sessions

Follow-up sessions with nurse focus on reviewing the participants exercise and weight loss goals and setting of new goals if appropriate. The performance of individual exercise will be checked and if necessary they will be corrected, progressed in terms of frequency and duration for aerobic exercise, load and repetitions for strengthening exercise or regressed if pain has increased as a result. Weight will be monitored at each session and the participant's efforts to lose weight discussed with nurse. Signposting to information and advice will be re-enforced as required.

The final session will include a review of goals with a focus on encouraging the participant to continue with long-term exercise adherence and continuing weight loss or healthy weight maintenance.

Additional File 3:
Additional information on research measures

MUSCLE FUNCTION TESTING:

Isometric strength of the knee extensor muscles will be determined (best of 3 attempts) during a static maximal voluntary contraction. Peak power output and fatigue will be determined during 20 maximal isokinetic knee extensions at an angular velocity of 90°/s, which ensures all muscle fibres of the quadriceps muscle group are recruited [34]. All muscle function testing will be performed using an isokinetic dynamometer (HUMAC Norm, CSMi Solutions, MA, US).

QUANTITATIVE SENSORY TESTING (QST):

Pressure pain threshold (PPT)

PPT involves gently pressing on one place with a small handheld instrument called an algometer. A finger-width, soft rubber probe gently presses down and gradually increases pressure. The participant presses a button to stop the test as soon as the feeling of pressure become one of pain. The algometer is removed as soon as the button is pressed. The PPT measurements may be performed 3 times each at 3 different places:- on the forearm (brachioradialis muscle), knee (medial joint line, inside surface of the knee) and leg muscle (anterior tibialis). The pain from PPT should be mild, as we are asking only about the first feeling of pain. Each PPT lasts for less than 30 seconds. The participants will be familiarised with the test before it is administered so that they know what to expect and how we would like them to respond.

Temporal summation (TS)

TS involves a blunt metal wire with a small weight attached that has been built into a pen-shaped device, and this is applied to the skin. The feeling is one of sharpness, but the skin is not broken. The test is applied 5cm above the knee cap, on the skin at the bottom of the front of the thigh. The participant is stimulated once by the device and asked to rate their pain/discomfort from 0-10. They then have 10 applications in the same place, at a rate of 1 per second, and are asked to rate the average feeling. Two TS measurements will be done. A large majority of healthy participants and people with knee pain rate pain as less than 4/10 from TS, and each TS measurement lasts for less than 30 seconds. The given scores will be noted.

Conditioned Pain Modulation (CPM)

PPT will be measured on the proximal anterior tibialis. A manual blood pressure sphygmomanometer will be applied to the opposite upper limb, and inflate to above the systolic pressure. The participant will squeeze a ball in their hand and inform researcher once the pain or discomfort in the upper limb reaches 4/10. PPT will be measured at the proximal anterior tibialis anterior as described earlier.

Additional File 4:
Collection and storage of biological samples

TRANSPORT AND STORAGE OF THE TISSUES

Whole blood (5ml) samples will be stored in a freezer (at -20°C) prior to DNA and RNA extraction. Remaining blood (5ml) will be centrifuged as soon after venesection as possible and the serum stored at -70C within freezers in the University of Nottingham Clinical Sciences Building (CSB), City Hospital for future metabolomic studies. Excess samples (DNA, serum, Paxgene for RNA extraction) that remain after the study analyses have been undertaken will remain stored within the CSB for possible future research studies related to OA and/or pain provided that participants are agreeable and sign the optional clause on the consent form. These CSB facilities come within the remit of the Research Tissue Bank (DI Dr William Dunn- Licence Number 12265). Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2004.

Samples will be stored in linked anonymised format in the CSB and labelled using a randomly generated unique participant identifier to permit accurate linkage to clinical data and the consent form. The master database will be held by Dr Abhishek in a password encrypted file.

Laboratory Analysis

Peripheral blood for measuring Lipid profile, HbA1c and CRP will be sent to the Clinical Pathology Department of the Nottingham University Hospitals NHS Trust.

Whole peripheral blood will be sent from the University of Nottingham to a specialist company or academic partners for DNA and RNA extraction . All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. The RNA will be used to identify genetic changes that result from receiving the intervention. The DNA will be used to find any causal variants that explain the response to treatment. It will be explained to the study participants that giving blood for DNA and RNA extraction is optional. Similarly, serum or plasma may be sent to other academic or commercial entities for biochemical analyses . Such analyses will be undertaken on anonymised samples under usual Material Transfer Agreement arrangements The companies would also require a HTA licence for research unless this is being undertaken as part of this research study, or the bloods are being processed to render the samples acellular within 7 days of their receipt or a new ethics application was submitted.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	___4_____
Protocol version	3	Date and version identifier	___2_____
Funding	4	Sources and types of financial, material, and other support	__24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,_24_____
	5b	Name and contact information for the trial sponsor	___24_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___17_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____N/A*_____ (as feasibility study)

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11,12 additional file 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	additional file 2
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_8, 12, 13, 14 additional files 1, 3

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Figure 2 Table 1 p11 Table 2 p13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__14 _____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ 6___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A_____ (as unblinded)
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 12, 13, 14 additional file 1, 3 and 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___15_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____15_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_ 8 9, 15___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15 N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A 15____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____14_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____16_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	additional file 5_
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	additional file 5

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	additional file 4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.