The PROP OA Trial Protocol

Full title: A multi-centre, primary care, randomised, parallel-group, superiority trial (with internal pilot) to evaluate the effectiveness of bracing in the management of symptomatic knee osteoarthritis: the PROP OA trial

Short title: PROvision of braces for Patients with knee OsteoArthritis (PROP OA): a randomised controlled trial

RESEARCH REFERENCE NUMBERS

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Department of Health and Social Care disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

VERSION CONTROL

Version	Issue date	Reasons for amendments; additional changes
v2.0	24-Apr-2019	Copyright added, assessment of eligibility table updated, medical record review data removed from the Model-based health economic analysis (section 8.4.2)
v2.1	10-Jul-2019	Add detail on when eligibility criteria will be assessed

SIGNATURE PAGE

I agree to conduct the trial in compliance with the approved protocol, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date: 10-JUL-2019

Name (please print):

GEORGE PEAT

Sponsor statement:

Where Keele University takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

LIST of CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
CAG	Clinical Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention-to-Treat
MDC	Minimum Data Collection
MI	Motivational Interviewing
NICE	The National Institute for Health and Care Excellence
NJR	National Joint Registry
OA	Osteoarthritis
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Participant Information Leaflet
PPIE	Public and Patient Involvement and Engagement
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SMS	Short Message Service
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

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TRIAL SUMMARY

Trial Title	A multi-centre, primary care, randomised, parallel-group, superiority trial (with internal pilot) to evaluate the effectiveness of bracing in the management of symptomatic knee osteoarthritis: the PROP OA trial	
Internal Ref. Number (or short title)	PROvision of braces for Patients with knee OsteoArthritis (PROP OA): a randomised controlled trial	
Trial Design	Interventional Allocation: randomised; Intervention model: parallel-group; Masking: trial administrator, data entry administrator, trial statistician Primary purpose: Symptom control/reduction & reducing functional limitation Phase IV	
Trial Intervention (where applicable)	Off-the-shelf knee brace with adherence enhancing component added to 'Best Primary Care' (BP+B) *versus* Best Primary Care alone (BP)	
Trial Participants	Adults aged 45 or older with osteoarthritis of the knee	
Planned Sample Size	434	
Treatment duration	6 months	
Follow-up duration	12 months	
Planned Trial Period	1 Sep 2018 – 30 Nov 2022	
	Objectives	Outcome Measures
Primary	To determine, in adults with symptomatic knee OA, if BP+B is superior to BP for the composite score of patient reported pain, other symptoms, activities of daily living, function in sport and recreation and knee-related quality of life at 6 months.	KOOS-5
Key Secondary	If BP+B is superior to BP for KOOS-5 at 3 and 12 months. If BP+B is superior to BP for the separate components of the KOOS-5 at 3, 6 and 12 months. The cost-effectiveness of BP+B compared to BP.	KOOS-5 KOOS Pain, KOOS Other symptoms, KOOS Activities of Daily Living, KOOS Function in Sport and Recreation, KOOS Quality of Life EQ-5D-5L, knee OA-related resource use

PLAIN ENGLISH SUMMARY

AIM(S) OF THE RESEARCH: To show whether wearing a knee brace provides more relief for people with painful osteoarthritis of the knee than just having best primary care (education, advice and exercise), and whether this is good value for money for the NHS.

BACKGROUND: Osteoarthritis of the knee is very common. It causes pain, problems with walking and movement, and can make daily life very difficult. There is no cure for osteoarthritis, but with treatment, symptoms can be improved allowing people to stay active. Wearing a knee brace could help patients with

osteoarthritis of the knee by reducing the load going through the joint and improving its stability. However, there are mixed reports about whether wearing a knee brace does actually help.

DESIGN AND METHODS: We will complete a trial with 434 adults aged 45 or older with osteoarthritis of the knee. We will identify patients after they have consulted their GP with knee pain, by screening physiotherapy referrals in NHS services in Staffordshire, Cheshire, Greater Manchester, and Northumbria, and by asking people to volunteer following social media and other advertising.

All participants in the trial will get "best primary care". This includes a 20 minute appointment with a physiotherapist who will give them education about knee osteoarthritis and the benefits of exercise, physical activity and weight loss, advice about how to relieve knee pain, and a knee exercise programme. They will also be given an information booklet. Half of the participants will also get a knee brace that will be checked by the physiotherapist 2 weeks later. The type of brace they get will be based on the physiotherapist's assessment and X-ray findings. They will be supported to keep wearing the brace for at least 6 months. This includes text message support to help them with use of the brace.

Participants will be asked about their pain and symptoms after 3, 6, and 12-months to see whether the knee brace was a useful addition to best primary care. We will ask participants if we can look at their medical records to see if wearing the knee brace has reduced the need for surgery. We will interview some participants to find out more about using the knee brace and whether they followed the advice they had from physiotherapists.

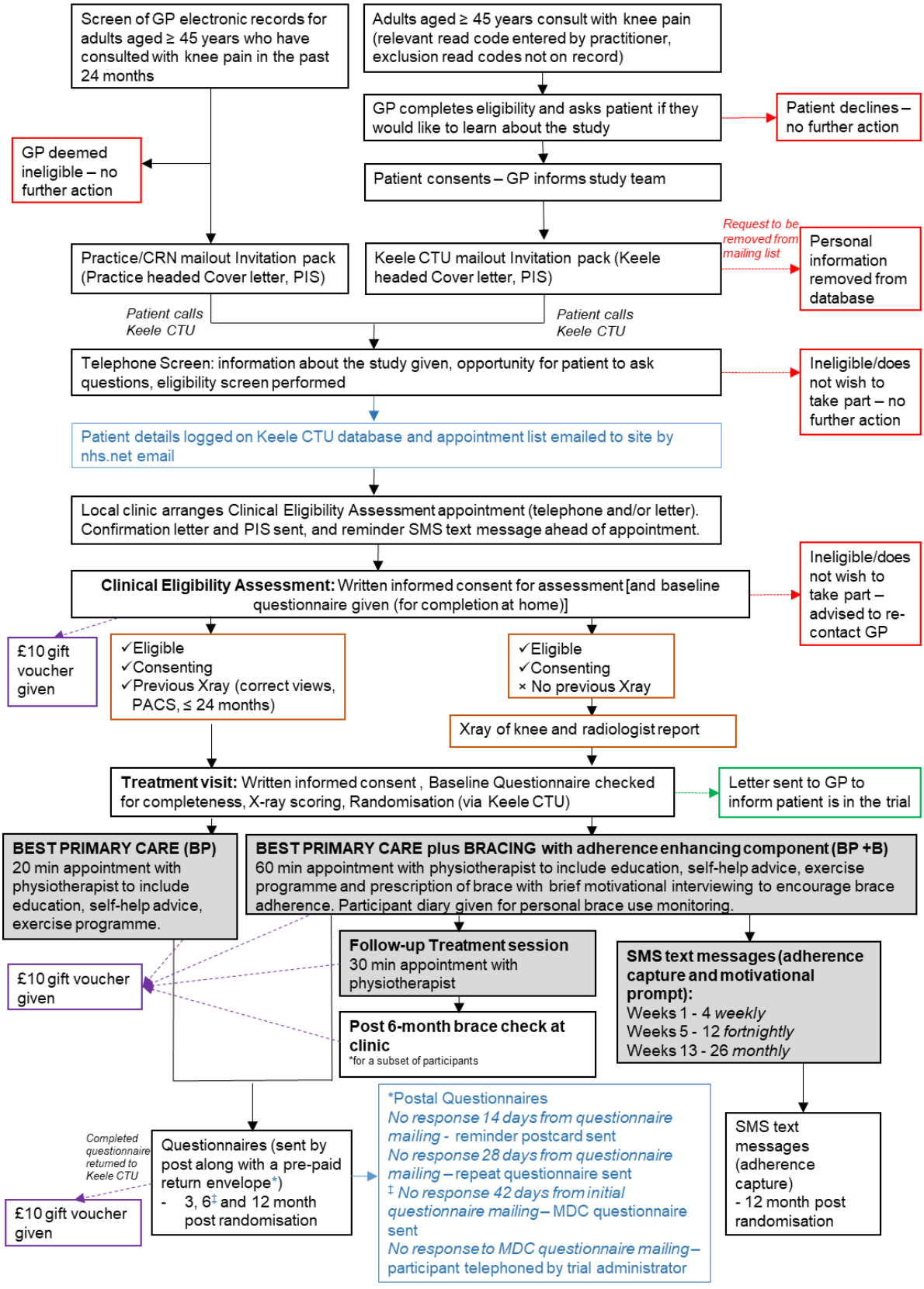
PATIENT AND PUBLIC INVOLVEMENT: Patient representatives will be involved at every stage of the trial. Two patient representatives have joined the study team, and have jointly written this summary. Five patient representatives with knee osteoarthritis also helped in the design of the trial by taking part in a workshop. For example, they helped to decide how pain and symptoms should be measured. Patient representatives continue to be involved by helping to develop the content of text messages to support brace use, monitoring trial progress, helping to understand interview findings, and developing and delivering messages about the trial findings that are easily understandable to the general public.

DISSEMINATION: We will present the findings at national and international meetings, and publish the trial results in high-quality medical journals. We will also show the outcome of the trial on our University and osteoarthritis websites (for example Versus Arthritis), and in GP practices, which all patients will be advised to look at. Articles about the trial will also be written for local magazines, newspapers and radio stations.

TRIAL FLOW CHARTS

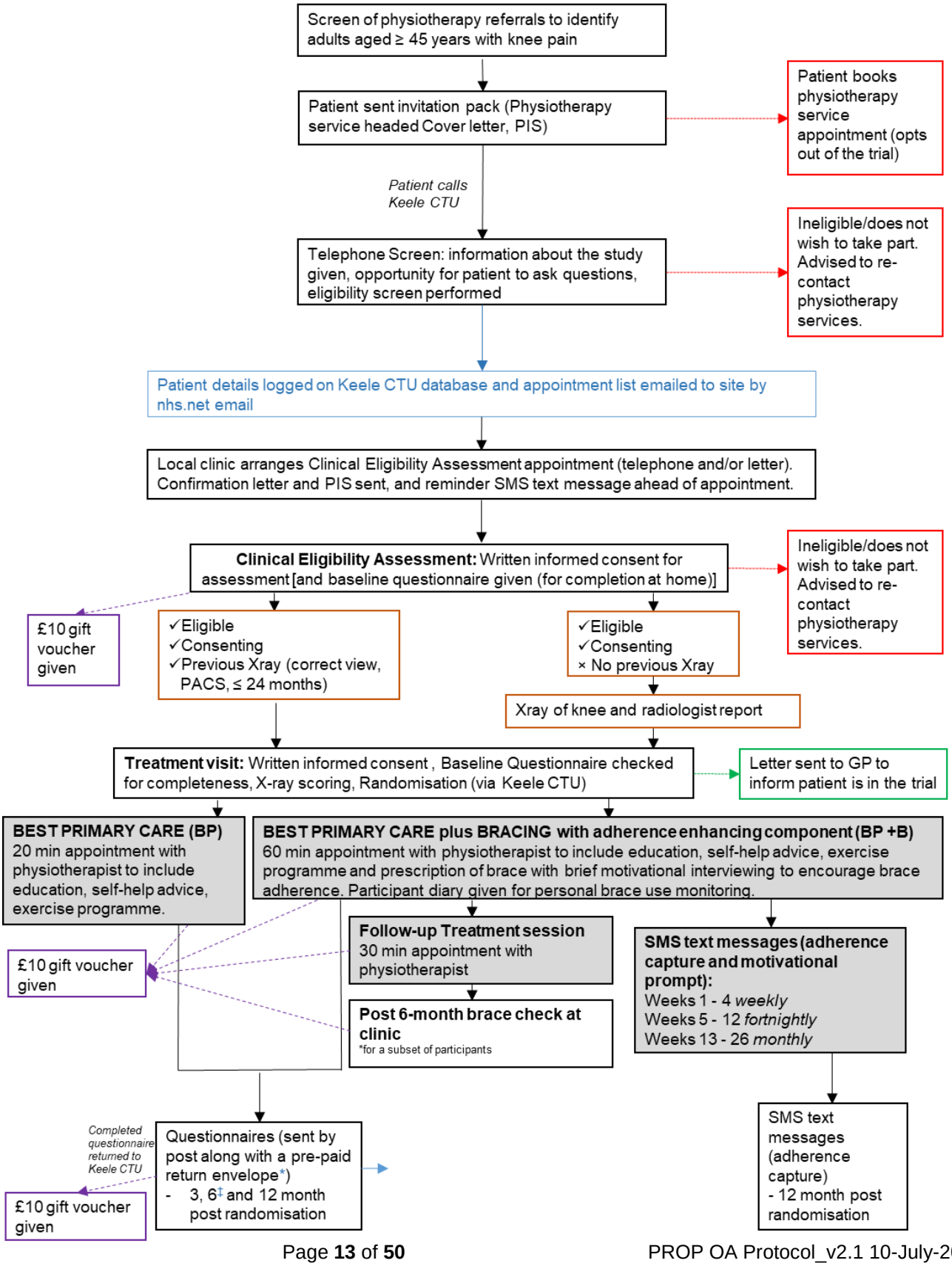
PROvision of braces for Patients with knee OsteoArthritis (PROP OA): a randomised controlled trial

Recruitment method 1: GP consulters



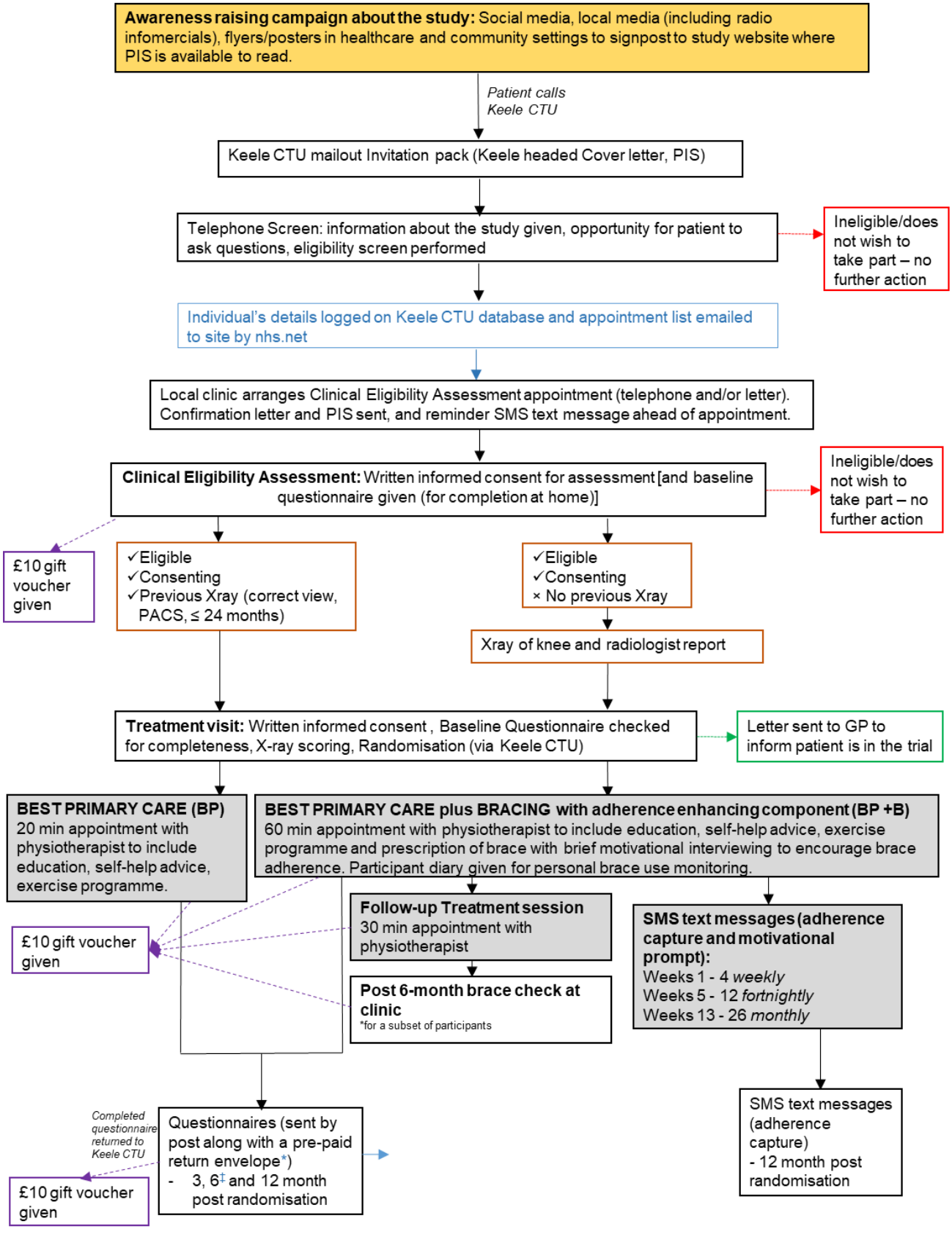
PROvision of braces for Patients with knee OsteoArthritis (PROP OA): a randomised controlled trial

Recruitment method 2: Physiotherapy referrals



PROvision of braces for Patients with knee OsteoArthritis (PROP OA): a randomised controlled trial

Recruitment method 3: Self-referral from the community



1 BACKGROUND

Symptomatic knee osteoarthritis affects an estimated 10% of adults aged over 55 years[1] and has a significant impact on population health, healthcare demand, and societal costs. Trends in disability-adjusted life-years attributed to osteoarthritis,[2] the number and rate of primary knee replacements,[3-6] and rates of new presentations to primary care[7] all suggest an increasingly common problem that accounts for up to 0.5% gross domestic product in high-income countries.[8,9]

In the United Kingdom, NICE currently recommends that people with OA who have "biomechanical joint pain with or without instability should be considered for assessment for bracing as an adjunct to their core treatments".[10] However, there remains a lack of high-quality trials on their efficacy and effectiveness and this is reflected in international sources of clinical guidance, some of which recommend bracing for knee OA,[11,12] while several others have been unable to make a recommendation.[13-16]

It is difficult to gauge the current demand for, and use of, braces among people with knee osteoarthritis. Previous UK population and primary care surveys of treatment use among patients with knee osteoarthritis do not contain information specifically on use of braces[17-22] although the study by Porcheret et al.[18] suggested fewer than 5% of patients presenting to primary care would have a brace offered to them as a treatment option; similar to a previous US estimate.[23] In a UK national survey conducted in 2006, only 69 physiotherapists out of the 538 (13%) who had treated a patient with knee OA in the last 6 months reported advising a knee brace.[24] A further challenge is the wide range and types of braces available. Over 1000 are listed in the NHS suppliers catalogue, and published studies have covered 35 types of brace from 13 different manufacturers.[25]

1.1. Mechanism of action

Braces can be either custom-made or off-the-shelf, and have been broadly classified into unloader braces and soft (sleeve) braces (rest orthoses are not further considered here).[26] Knee osteoarthritis is presumed to be largely mechanically driven and braces are designed as a biomechanical intervention even though their mechanisms of action may be broader (e.g. increasing confidence in the knee).[27]

Several biomechanical mechanisms of action have been proposed.[28-30] Formal investigation of these, with a few recent exceptions, has been limited to valgus unloading braces for medial tibiofemoral joint osteoarthritis. Mechanisms of action that rely on increasing joint stability, lessening muscle co-contraction, and improving proprioception are plausible but direct evidence appears limited. Stronger evidence relates to the effect of valgus unloading braces on reducing the knee adduction moment (KAM) during level walking, and changing the distribution of load and decreasing the magnitude of load on the knee through improvements in malalignment.[28,29] Patella sleeve braces may increase the contact area between patella and femoral trochlea potentially reducing patellofemoral joint contact stress.[31]

The extent to which the magnitude of changes is clinically significant and translates into reductions in patient reported pain and functional limitation and improved observed functional performance and activity levels is less clear.

1.2. Evidence on the effectiveness of braces for knee osteoarthritis

A Cochrane review, originally published in 2005[32] and updated in 2015,[33] identified five RCTs,[34-38] with sample sizes ranging from 33 to 117 randomised participants, that had compared any type of brace for OA of the knee against no treatment or other treatment such as restricted activity, patient education, physiotherapy, pharmacological treatment and orthoses or surgical treatment. The review concluded that "low-quality evidence suggests that people with OA who use a knee brace may have little or no reduction in pain, improved knee function and improved quality of life."

Five further relevant systematic reviews[16,28,30,39,40] and one narrative review[41] have since been published that identified a total of 13 additional RCTs,[42-54] partly due to different eligibility criteria from the Cochrane review (e.g. including crossover designs), two of which were published after the Cochrane review[53,54] and had

randomised 126 and 52 participants respectively. A search of the WHO International Clinical Trials Registry Platform Search Portal identified one additional small (n=10) trial in the UK of 3D printed braces for medial knee OA that is completed but yet to report (ISRCTN43076496).

These recent systematic reviews have concluded either that the existing evidence is insufficient,[16,39,40] or is consistent with small-to-moderate effects on pain and functional limitation for unloader braces[28] and soft (sleeve) braces[30] that warrant further investigation. Only three trials[35,36,42] and one observational study[55] followed participants up for 6 months or longer.

Effect sizes from individual RCTs vary depending on the study design, and previous reviews emphasise the importance of choice of control intervention,[28] the challenges in specifying a suitable placebo control for efficacy trials,[56] and difficulties in achieving adequate patient and clinician blinding.[28] There is also considerable heterogeneity in the nature of the intervention and the "dose" of brace use varies from one trial to another.

Given the heterogeneous 'dose' of brace use prescribed, adherence is difficult to judge but has been broadly reported in clinical trials as ranging between 45-100%.[28] However, self-reported estimates from audits and clinical trials of unloader braces suggest that between a half and three-quarters of patients are no longer regularly using their brace at one year - defined as at least one hour for 2 or more days per week.[35,57] Lack of effect, difficulties donning/doffing the brace, and adverse reactions are the reasons given for discontinuation with up to 25% of trial participants allocated valgus unloader braces reporting discomfort, swelling, blisters or skin irritation, mostly secondary to poor fit.[28] Levels of adherence and discontinuation of soft braces is less well-documented. Participants in one trial reported wearing soft braces for patellofemoral joint OA for an average of 7.4 hours per day at 6 weeks.[53] Soft (sleeve) braces may get hot and sweaty causing skin irritation and poor fit again may cause discomfort. Brace wear does not appear to reduce thigh muscle strength.[58,59]

2 RATIONALE

This trial was designed in response to a commissioned call from the NIHR Health Technology Assessment programme (16/160). Our proposal directly addresses the call for an efficient and pragmatic randomised controlled trial (RCT) with an internal pilot phase and clear stop/go criteria to the main trial (with adherence being one of the pilot phase success criteria) to investigate in primary care, the clinical and cost-effectiveness of knee braces in the management of knee osteoarthritis (OA). We are proposing a large, simple, 2-arm RCT in a wide target population with intervention patients matched by clinical and radiographic indication to knee brace type (patellofemoral, tibiofemoral unloading, or neutral stabilising). This mirrors a pioneering NHS primary care-based bracing service for the provision of braces for patients with OA, set up in 2005 and run by the Musculoskeletal Interface Service within Cornwall Partnership NHS Foundation Trust.

Choice of setting. Intervention and comparator treatments will be delivered in NHS physiotherapy services. To our knowledge there are few current primary care NHS services in England that provide braces for knee OA. Physiotherapists may be well-placed to offer this. They are the largest group of NHS musculoskeletal healthcare providers, and are increasingly the first point of contact for these conditions. Further evaluation of direct self-referral and on-site physiotherapy to improve access to this has been recommended by the Primary Care Workforce Commission and fully supported by Health Education England.[60] NICE recognises the potential role of physiotherapists in bracing for OA.[10] Physiotherapists delivering interventions will receive training that includes the assessment and correct fitting of the braces selected for this trial. Based on PPIE feedback, for the convenience of participants, interventions will be provided within PROP OA knee pain clinics, a model successfully used by our research team in several studies of treatments for musculoskeletal pain conditions in primary care (STarT Back trial,[61] ATLAS cohort study,[62] HTA SCOPiC trial[63]).

Choice of population. Our target population are adults with knee osteoarthritis with significant pain on weight-bearing activities with or without instability (buckling). This aligns with NICE guidance on the indications for bracing.[10] All trial participants will have clinically significant knee pain on weight bearing (e.g. walking or going up and down stairs) of at least four out of 10 on a numerical rating scale, designed to be broadly representative of the wider primary care population in whom bracing could be considered.[10,64] Current NICE

guidance[10] recommends clinical rather than radiographic criteria for diagnosing OA in primary care practice and this is reflected in our eligibility criteria. We have successfully used this approach in previous primary care trials of knee OA.[65-67] Within our sample we are able to identify individuals with predominant patellofemoral, tibiofemoral, or no clear compartmental involvement, diagnosed clinically and radiographically, and those with and without knee instability (buckling) for planned subgroup analyses and for potential future pooling of trial datasets (OA trial bank (www.oatrialbank.com)[68,69]).

Choice of interventions. For an efficient trial design and future practical service provision within the NHS we had to narrow the range of braces that would be included in this trial whilst trying to ensure sufficient flexibility and choice for physiotherapists and patients. Based on previous trials, mechanistic studies, expert advice, PPIE feedback, and feasibility for provision in NHS primary care, we selected an off-the-shelf patellofemoral brace, a first- and second-choice tibiofemoral unloading brace, and a neutral stabilising brace. Participants will be matched to brace type based on clinical examination and X-ray findings. As no robust guidance exists regarding optimal brace dose,[57] based on expert opinion, experience, and Clinical Advisory Group (CAG) feedback, we have taken an individualised approach based on holistic assessment. Participants will be advised to wear the brace on painful weight-bearing activity (e.g. walking, going up and down stairs), with a starting minimum usage of 1 hour on two or more days per week (the value chosen by Squyer et al as indicating 'regular brace use'[57]), gradually increased based on tolerance to wearing the brace on all painful weight-bearing activity up to a maximum of 8-12 hours per day. Individuals will be advised to wear the brace for 6 months, and continue to wear it beyond this time if they find it beneficial.

An emphasis on enhancing adherence. Without additional strategies, adherence to brace use may be low.[28] Barriers and facilitators to adherence to knee brace use among individuals with knee OA are currently under-explored. However, practical issues (for example, brace discomfort, poor fit, skin irritation),[57] and participants' attitudes and beliefs (for example, thinking that the knee brace will not help or not liking the look of the brace) appear important from existing literature,[57] and PPIE and CAG feedback. Our intervention is therefore designed to address these important issues and integrates simple, affordable, previously successful,[70,71] acceptable,[72,73] theory-driven[74] approaches to enhancing adherence to brace use. With regards to practical issues, comfort of knee braces will be addressed, for example, straps will be cut and rounded, and hinges will be contoured for each individual. Participants will be provided with oral and written advice about how to care for their brace, and what to do in the event of skin irritation. Participants will have the fit of their brace reviewed at two weeks by a physiotherapist. If a participant refuses the TF unloading braces (which our PPIE group perceived to be the bulkiest and least aesthetically appealing brace type), they will be offered a neutral knee stabilising brace. To build participants' intrinsic motivation and resolve ambivalence about adhering to brace use,[70] the intervention also contains brief motivational interviewing (MI) techniques and motivational prompts, matched to level of reported frequency and duration of brace use, sent to participants via SMS text message for 6 months.

Evaluating adherence. Adherence to brace use at 3 months is a progression criterion for our internal pilot. However, it is anticipated that simple self-report questions administered in postal questionnaires are unlikely to be provide a sufficiently accurate measurement of adherence. We will collect information on brace use by participant responses to SMS text message over the first 6 months of follow-up and again at 12 months. [redacted] Based on PPIE feedback, findings from an embedded qualitative study exploring participants' adherence to brace use will be made available at the time of judging the success of the internal pilot. For example, it will be important to know if low adherence to brace use is due to symptom improvement, so participants feel they do not need to wear the brace, or whether this is due to discomfort or cosmetic reasons.

Choice of comparator. As our focus is on effectiveness rather than efficacy, no sham brace is included. The trial comparator is 'Best Primary Care' - a single, face-to-face consultation with a physiotherapist that, in line with NICE core treatment recommendations for OA,[10] and based on findings from a clinical examination

includes: education, simple self-help advice on pain management, and a lower limb exercise programme to be completed at home.

Choice of outcomes. Important outcomes in the Commissioning Brief were function, quality of life, and activities of daily living. PPIE feedback additionally stressed the importance of pain reduction, and so we have chosen as the primary outcome a composite score of pain, other symptoms, activities of daily living (ADL), function in sport/recreation and knee-related quality of life (the composite Knee Injury and Osteoarthritis Outcome Score (KOOS-5).[76] Composite KOOS scores have been used as the primary outcome in RCTs of knee replacement,[77] surgical and non-surgical intervention for degenerative meniscal tears,[78] and limb realignment surgery[79] but typically with removal of the ADL score (KOOS-4). Given the interest and relevance of ADL we have chosen the KOOS-5 but will have KOOS-4 (for external comparisons) plus each of the subscale scores being key secondary outcomes. All outcome domains are measured using tools recommended for trials in this field.[56,64,80-82] We will collect outcome measures at 3, 6 and 12 months. Six months was chosen as the primary endpoint. To enable the future longer-term effects of knee bracing on the time to, and receipt of, knee surgery (knee arthroscopy and knee joint replacement) to be explored, we will seek consent from participants for linkage to Hospital Episode Statistics, National Joint Registry (NJR) and primary care electronic health record review.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The overall aim of the trial is to determine the clinical and cost-effectiveness of adding knee bracing (matched to patients' clinical and radiographic presentation and with adherence support) to Best Primary Care (BP+B) compared to Best Primary Care alone (BP), in adults with symptomatic knee OA.

3.1 Primary objective

To determine, in adults with symptomatic knee OA, if BP+B is superior to BP for the composite score of patient reported pain, other symptoms, activities of daily living, function in sport and recreation and knee-related quality of life (KOOS-5) at 6 months.

3.2 Secondary objectives

Key Secondary Objectives

To determine, in older adults with symptomatic knee OA:

3.2.1. If BP+B is superior to BP for KOOS-5 at 3 and 12 months.

3.2.2. If BP+B is superior to BP for the separate components of the KOOS-5 (patient reported pain, other symptoms, activities of daily living, function in sport and recreation and knee-related quality of life) and pain on weight-bearing activity NRS at 3, 6 and 12 months.

3.2.3. The cost-effectiveness of BP+B compared to BP.

Other Secondary Objectives

3.2.4. Determine, in adults with symptomatic knee OA, if BP+B is superior to BP for: self-reported pain; instability (buckling); treatment response; physical activity; social participation; arthritis self-efficacy.

3.2.5. Determine the safety of knee bracing in adults with symptomatic knee OA ((serious) related adverse events).

3.2.6. Understand the acceptability and experiences of the trial procedures and interventions (BP and BP+B) to participants and physiotherapists receiving and delivering the trial interventions.

3.2.7. Explore adherence to the interventions, including the barriers and enablers of adherence to brace use in participants allocated to BP+B.

3.2.8. Determine how often clinician's judgement on the appropriate brace type is changed by plain X-ray findings.

A priori exploratory subgroup analyses will be completed to explore the effectiveness of BP+B vs BP by: (a) predominant compartmental involvement, (b) presence of knee buckling, (c) level of adherence, (d) presence of anxiety/depression.

3.3 Outcome measures/endpoints

To facilitate comparison and pooling of our results with previous trials, we have selected outcomes to reflect domains and measures recommended for trials and meta-analyses in OA (OMERACT[83]), knee OA,[56,64,80] and chronic pain (IMMPACT[81,82]), identified partly through the COMET database[84]) and recent systematic reviews (e.g.[30]). The psychometric properties of the primary outcome measure have been extensively investigated.[85] Furthermore, several factors recommended for patient stratification/phenotyping in OA/chronic pain trials[86,87] will be collected, including severity and compartmental distribution of knee OA and concomitant anxiety/depression. Of specific interest in the current trial is the presence of knee instability which NICE suggest may be an indication for brace use. We will focus on buckling which will be ascertained by single items developed in the Multicentre Osteoarthritis Study (MOST).[88,89]

The end points are defined as:
- Primary end point at 6 months for clinical effectiveness and at 12 months for cost effectiveness analysis
- Withdrawal due to any reason

3.4 Primary endpoint/outcome

The primary endpoint for clinical effectiveness is at 6 months. The primary outcome is patient-reported composite knee score of patient reported pain, other symptoms, activities of daily living, function in sport and recreation and knee-related quality of life (KOOS-5).[76]

3.5 Secondary endpoints/outcomes

Secondary clinical outcomes: Secondary outcomes include patient reported pain, other symptoms, activities of daily living, function in sport/recreation, and knee-related quality of life (KOOS subscales),[76] pain (pain on weight-bearing activity (NRS)), intermittent and constant pain (ICOAP)[90]; instability (buckling)[88]; OMERACT-OARSI responder criteria[91,92]; physical activity (International Physical Activity Questionnaire - Elderly (IPAQ-E)[93]; social participation (PROMIS)[94,95]; arthritis self-efficacy[96]; treatment acceptability[97]; (serious) related adverse events. KOOS Pain items contain those needed to score WOMAC Pain, KOOS Activities of Daily Living (ADL) score is the same as WOMAC Physical Function score, and KOOS-4 can be easily computed: all of which permits wider comparison of findings and facilitates future IPD meta-analysis.

Cost effectiveness: Outcomes to evaluate cost effectiveness include the EQ-5D-5L questionnaire[98] and self-reported knee OA-related resource use (primary care visits, (e.g. GP, nurse, physiotherapy), visits to other health care professionals, prescribed analgesics, tests and investigations, other treatments (e.g. injections), secondary care consultations, inpatient stays and surgery). Data will be collected within the trial on the duration of the initial face-to-face physiotherapy visits for BP and BP+B, the clinical grade of physiotherapists delivering the interventions, and the brand and type of braces used so that the cost of BP and BP+B can be calculated. Unit costs from standard UK sources will be sought for all health care resource use items. Data on broader costs will also be collected, related to both out of pocket costs (e.g. over-the-counter medications), private health care and time off work to calculate productivity losses. Information on occupation, further details of typical work activities and the nature of their employment (full time or part time) will be requested. The average wage for each respondent will be identified using UK Standard Occupational Classification coding and annual earnings data for each job type.

Time to and receipt of knee surgery (knee arthroscopy and knee joint replacement): All participants will be invited to consent to linkage of their trial data to the Hospital Episode Statistics and National Joint Registry (NJR) and medical record review for receipt of knee arthroscopy and knee joint replacement.

Adherence: Measuring adherence to non-pharmacological interventions is challenging. Self-reported measures of adherence are the simplest, least expensive option, however may lead to adherence being over-estimated, recall over extended periods inaccurate, and monitoring may in itself serve as an adherence-enhancing intervention.[99,100] Within this pragmatic trial, the simplest way to measure adherence to brace use is via self-report using similar language to that we have used in previous trials of non-pharmacological care for OA.[65,67] Data will be captured via SMS text message on a fixed, tapering schedule over the first 6 months of

follow-up, with a text message also at 12 months to evaluate longer-term adherence. Patient self-report is relatively simple to collect but objective measures can also be used to capture more detailed, potentially more accurate adherence data.[10] However, there is little evidence on their use across multiple brace types. [redacted]

Adverse events: Adverse events, including skin irritation from the knee brace, will be captured through case report forms (CRF), and direct contact between the CTU and the participant, their PROP OA physiotherapist, GP or the Site PI.

3.6 Exploratory endpoints/outcomes

Consent will be sought from participants for linkage to Hospital Episode Statistics and National Joint Registry to permit future longer-term evaluation of effect of braces on postponing or preventing the need for knee surgery.

4 TRIAL DESIGN

4.1 Interventions/Treatments

Comparator: Best Primary Care (BP)
Participants randomised to receive BP will receive a single, face-to-face, 20-minute consultation with a physiotherapist that, in line with NICE core treatment recommendations for OA,[10] and based on findings from a clinical examination (performed within the 'Clinical Eligibility Assessment' (see section 7.1), will include: ***education*** regarding pathogenesis and prognosis of knee OA, and the benefits of exercise, increasing physical activity and weight loss; ***simple self-help advice on pain management***, including home-use of heat/cold, pacing of activities and simple analgesia; and a ***lower limb exercise programme*** to be completed at home, focusing on muscle strengthening, knee range of movement and proprioception. Supporting the advice given during the face-to-face consultation, participants will also be provided with high quality written material, and a print out of their exercise programme to facilitate their exercise practice at home. This is modelled on the 'usual care' intervention from our previous BEEP trial.[67]

Intervention: Best Primary Care plus Bracing with Adherence Enhancing Component (BP+B)
Participants randomised to receive BP+B will receive a one-hour face-to-face initial treatment session with a physiotherapist, a 30 minute face-to-face follow-up appointment with the same physiotherapist 2 weeks later, and motivational prompts to enhance brace adherence sent via SMS text message over the first six months of follow-up.

Initial Treatment Session
Participants will receive BP as described above, plus brace and adherence enhancing components.

Knee brace: In addition to BP, participants will be recommended either a patellofemoral, tibiofemoral unloading, or neutral stabilising knee brace according to their pattern of knee OA (predominantly patellofemoral OA, tibiofemoral OA (medial/lateral), or generalised knee OA) based on clinical assessment (performed by the physiotherapist during the 'Clinical Eligibility Assessment' (see 7.1) and plain X-ray findings (read for red flags by NHS radiologist then read for compartmental severity of osteoarthritis by trial physiotherapists), but also taking into account current and desired level of physical activity, ability to don/doff brace, willingness to wear the brace type, and immediate symptom response when the brace is tried on and tested in clinic. Braces will be fitted to ensure maximum comfort (e.g. hinges contoured, straps adjusted and cut to match participants' body shape and size). Dose of brace use will be individually tailored. Participants will be advised to wear the brace on painful weight-bearing activity, with a starting minimum usage of 1 hour on two or more days per week, gradually increased based on tolerance to wearing the brace on all painful weight-bearing activity up to a

maximum of 8-12 hours per day. Individuals will be advised to wear the brace for 6 months, and continue to wear it beyond this time if they find it beneficial. Verbal and written information will be provided on brace application and care, including cleaning instructions and what to do in instances of slippage, discomfort or skin irritation (e.g. blisters). Participants will be advised to contact the clinic if experiencing severe discomfort/skin irritation, and this information will be logged and reported. Supporting patient material (e.g. written information, short video clips) on brace application produced by the brace manufacturers will be available to support participants. The braces selected for use in this trial are from the two most-referenced manufacturers in the medical literature ([redacted])[25] and the manufacturer of the patellofemoral brace ([redacted]) previously demonstrated to be clinically effective in a similar population as intended with the current trial.[53] The braces, by type, are: patellofemoral – [redacted][1]; tibiofemoral unloading – [redacted]; neutral stabilising - [redacted]. These have been selected to provide an appropriate brace within each brace type, based on previous trial experience and evidence, PPIE feedback, and expert opinion (including CAG members' views).

Adherence enhancing intervention: Brief MI will be used to build participants' intrinsic motivation and resolve ambivalence about adhering to brace use.[70] The structure of the brief MI component will be based on published brief strategies to enhance motivation to change[70] and will be dovetailed alongside delivery of the knee brace. Brief MI will include both communication strategies and motivational techniques. Communication strategies include: a) open-ended, unstructured questions asking the patient to think, reflect, and provide their opinions and feelings about adherence to brace use in a comfortable non-judgemental atmosphere; b) use of affirmations or statements by the physiotherapist that recognises participants' strengths and assists in creating a rapport; c) reflective listening, i.e. the physiotherapist will demonstrate that they have heard and understood the participant by reflecting what they have said as well as strategically providing reflections to handle resistance to change and to help patients move along the continuum of change; and d) the physiotherapist will use summaries strategically to help resolve ambivalence and highlight the patient's self-motivational statements. Motivational techniques include a) helping the patient weigh the costs/benefits of adherence, b) providing education and feedback on adherence using the 'elicit-provide-elicit' process, c) exploring barriers and facilitators of motivation to adhere and confidence to adhere, and d) discuss how adherence can enhance, rather than detract from, things they most highly value (values clarification). Towards the end of the treatment session the participant will be provided with a diary which they can use to record whether they have worn the brace, for how long, if not what were the barriers to wearing the brace, and what are the possible solutions to those barriers. The purpose of the diaries is as a self-monitoring tool for participants and not as a source of data for evaluating trial outcomes or processes.

Follow-up treatment session

Two weeks after the initial treatment session participants will return for a 30-minute follow-up consultation. During this time the physiotherapist will check response to, and fit of the brace. For participants tolerating it well and finding it helpful, brace use will be progressed (e.g. advised to wear the brace for longer durations of painful weight bearing activity). If participants are experiencing discomfort or not finding it helpful, braces will be adapted (e.g. by adjusting the brace fit or providing further advice on appropriate brace dose). In extreme cases, if the brace is not tolerated it may be changed (most likely from a tibiofemoral unloading to neutral knee stabilising brace). If participants continue to not tolerate the knee brace or experience ongoing discomfort or skin irritation, they will be advised to contact the clinic who will provide appropriate advice, which may include discontinuing with any brace use. This information will be logged and reported. Adherence to brace use will also be reviewed and addressed using MI techniques and based on information provided within the brace diary.

Motivational prompts to enhance brace adherence

Motivational prompts to encourage adherence to brace use will be sent to participants via SMS text message. These will be matched to the level of brace use reported by the participant by SMS text message (low, mid, high). Motivational prompts will be sent weekly for the first 4 weeks, every fortnight for 8 weeks, and then monthly until the end of the intervention period at 6 months. Text messages will be administered using software

[1] [redacted]

developed by Keele CTU that has been used successfully in previous RCTs (iPOPP pilot trial,[72] HTA SCOPiC trial[63]).

4.2 Co-interventions

All participants will be advised that they can continue to access usual health care, including medications and consultations with other health professionals. Participants allocated to BP will be asked not to wear a knee brace for the 6 month period following randomisation. Details of co-interventions will be recorded in follow-up questionnaires.

4.3 Study Training

Physiotherapists: Physiotherapists delivering trial interventions will be representative of the range of physiotherapists that patients would see beyond the trial, i.e. Agenda for Change Band 5 or above. Participating physiotherapists will deliver both interventions and will receive a three-day face-to-face PROP OA training programme and additional remote training prior to the start of trial recruitment. This will cover all aspects of the trial including: clinical assessment; reading and interpretation of plain knee X-rays to judge which is the most severely affected compartment so as to inform brace allocation; provision of BP, and BP+B, including dovetailing the provision of knee braces with brief MI to facilitate adherence to brace use; [redacted] and GCP and trial procedures, including taking informed consent for research, completion of case report forms, and procedures for reporting adverse events and serious adverse events. Training materials developed by the brace manufacturers will be available to participating physiotherapists. In order to promote protocol fidelity, based on previous research,[101-107] best practice guidelines, and previous experience,[67,72] the training programme will be delivered using different strategies including interactive group discussion, problem solving, case examples, and role play. In addition, physiotherapists will receive a PROP OA manual (including detailed assessment and treatment protocol), a copy of which will also be available at each PROP OA knee pain clinic, and during the first three months of delivering the interventions, regular email reminders regarding the content of treatment sessions. At six months following the start of recruitment, a half day refresher session will be held, allowing physiotherapists to share best practice and discuss any challenges faced with other physiotherapists delivering the interventions. A further half-day refresher session will also be provided at one year. Treatment fidelity will be assessed by physiotherapist completed case report forms, and audio-recording or observation of clinic appointments, if deemed necessary.

Radiologists*:* Where a participant does not have a set of suitable recent knee X-rays accessible through PACS (the secure system used by the NHS to electronically store images like X-rays), plain knee X-rays (weight-bearing anteroposterior view, skyline and lateral view) will be taken according to standard NHS protocols at each site. Radiologists at each site will produce their standard report which will identify any potential radiographic red flags.

5 STUDY SETTING

Participants will be recruited from NHS general practice, physiotherapy services and from self-referral within the community following an awareness raising campaign. Interventions will be delivered within PROP OA knee pain clinics held in physiotherapy services at 4 NHS sites with on-site radiography departments within Staffordshire, Cheshire, Greater Manchester, and Northumbria. This will ensure sampling from a heterogeneous population spanning a range of area-level deprivation/affluence and a mixture of urban, semi-rural and rural areas.

6 ELIGIBILITY CRITERIA

The target population are adults aged 45 years and over with symptomatic knee OA, pain of 4 or more on 0-10 Numerical Rating Scale (NRS) during weight-bearing activity (e.g. walking, going up and down stairs), with or without knee buckling, who have no current or recent knee brace use but who would be willing to consider using a knee brace.

Eligibility criteria for the trial have been informed by conceptual/theoretical considerations, existing trial design recommendations,[56,64] previous trials and systematic reviews of bracing for knee OA,[33,53] and NICE OA clinical guidelines.[10]

Table 1. Eligibility criteria

Inclusion criteria	**How assessed**
Aged 45 years and over	GPS, TS
Residing in England	GPS, TS
Clinically significant knee pain on weight bearing (NRS >=4)	TS
With or without knee instability (buckling)	TS
Able to have knee x-ray	TS, CEA
Able to read and write English	TS
Access to a mobile phone that can receive SMS text messages	TS
Able to give full informed consent	CEA
Willing to participate	TS, CEA
Exclusion criteria:	
Red flags in the history or clinical examination that may indicate further investigation or referral for possible serious underlying pathology [NICE 5.1.1.[10]]	GPS, TS, CEA
Vulnerable individuals (e.g. in palliative phase of care for cancer, unstable mental health disorders)	GPS, CEA
Inflammatory/crystal arthritis (e.g. rheumatoid arthritis, gout, psoriatic arthritis)	GPS, TS, CEA
Significant neurological disorder (e.g. stroke, Parkinson's disease, multiple sclerosis, dementia)	GPS, TS, CEA
Fibromyalgia	GPS, TS, CEA
Symptoms not attributable to knee OA	CEA
Previous major surgery in the knee to be treated (partial/total knee replacement; high tibial osteotomy, NOT other previous arthroscopic surgery)	TS, CEA
Autologous cartilage implantation in last 12 months in the knee to be treated	TS, CEA
On the waiting list for TKR/THR within the next 6 months	TS, CEA
Unwilling to wear a knee brace	TS
Brace size unavailable for leg circumference	CEA
Knee brace contraindicated (superficial wounds where the knee brace would reside, psoriasis, eczema or poor circulation, arterial insufficiency, or severe varicosities that could result in skin at risk with regular brace wear, a history of thrombophlebitis in either leg)	CEA
Significant fixed flexion deformity that prevents fitting of brace	CEA
Injection in the knee to be treated within the last 3 months	TS, CEA
Recent/routine knee brace wear within the last 3 months	TS, CEA
Nursing home resident	GPS, TS
Unable to attend clinic	TS
Close family member already a trial participant	TS
Course of physiotherapy for the knee to be treated in the last 3 months	TS, CEA

CEA Clinical Eligibility Assessment; GPS Pre-mailout General Practitioner Screen; TS Telephone screening with the Trial Administrator

7 TRIAL PROCEDURES

7.1 Recruitment

Patient identification

In order to maximise recruitment, three methods will be used to identify potential participants, informed by our previous pragmatic trials of treatments for musculoskeletal pain conditions in primary care.[63,67,108] The three methods will proceed in parallel until the required sample size is reached. Participating general practices and physiotherapy services will be supported to assist with identification of potentially eligible participants through small payments to reimburse their time for screening patient lists.

Method 1 - Identification of General Practice consulters: Members of staff from the NIHR Clinical Research Network (CRN) or GP practice staff will screen electronic records of participating general practices for adults aged 45 years and over who have consulted with knee pain in the last 24 months. The electronic screen will identify patients based on knee pain related diagnostic or symptomatic Read Codes that were successfully used to identify adults with symptomatic knee OA in one of our previous RCTs (BEEP trial, n=514).[67] The electronic screen will also exclude those with a recorded serious pathology (e.g. inflammatory arthritis such as rheumatoid arthritis) and those in nursing home accommodation. GPs will be invited to screen the sample list and exclude those patients whom they consider inappropriate to be invited to participate in the trial.
To maximise recruitment, to capture prospective consulters, when a patient aged 45 years and over consults the GP with knee pain, and the GP enters an appropriate Read Code on the computer system, a 'pop-up' prompt screen will ask the GP if they think the patient would be suitable for consideration for the trial, taking into account the inclusion and exclusion criteria. Entering 'yes' on the computer system will flag the patient thought to be suitable, and allows the GP to briefly inform the patient about the trial and gain consent for contact by the study team.
In the event of slower than expected recruitment we will increase the number of participating GP practices and increase the time period for previous GP consultation with knee pain from 24 to 36 months.

Method 2 - Screen of physiotherapy referrals: To capture potential participants who have either been referred from primary care, or self-referred to physiotherapy, CRN or physiotherapy staff will prospectively screen physiotherapy referrals to identify adults aged 45 years and over with knee pain potentially due to OA.

Method 3 - Self-referral from the community: Not all individuals with knee OA will consult about their knee problem. Therefore, to capture non-consulters, adults aged 45 years and over with knee pain who would be willing to attend a PROP OA knee pain clinic for assessment and treatment can self-refer for consideration for the trial. Local communities around each participating NHS service will be provided with information about the trial via an awareness raising campaign. Informed by our previously successful awareness raising campaign in the HTA EASE Back pilot trial[108] and PPIE feedback, potential participants will be directed to our study website which will contain the Participant Information Leaflet (PIL) through an awareness raising campaign that will include one or more of: social media (Facebook and Twitter), local radio (including radio infomercials) and newspapers, and flyers and posters in GP surgeries, physiotherapy practices, and community settings (for example, libraries, train stations, information boards in supermarkets, and adverts on buses). Potential participants will be advised to telephone the trial administrator to register their interest.

Screening

Cover letter and Participant Information Leaflet (postally-administered)
Identified individuals will be mailed a cover letter and PIL. If they are interested in participating they will be asked to telephone the trial team on a free telephone number.

Telephone screening

Whilst on the telephone, the trial administrator will check the telephone eligibility criteria (see Table 1) and will provide individuals with the opportunity to discuss the trial prior to deciding whether or not they would be willing to participate. Individuals who fulfil telephone eligibility criteria and are willing to participate in the trial will be contacted by their local PROP OA clinic to arrange an appointment for a Clinical Eligibility Assessment, and if applicable, knee X-rays. A letter of confirmation of this appointment will be sent to participants along with a second copy of the Participant Information Leaflet. A one-way SMS reminder text message will also be sent to participants ahead of their appointment. Ineligible individuals will be made aware of how to identify other potential opportunities to participate in research in their local area by the trial administrator whilst on the telephone.

Clinical Eligibility Assessment (with/without new X-rays)
At this visit the following activities will be undertaken:

Confirmation of eligibility assessment by a PROP OA-trained physiotherapist. This will include undertaking a standardised clinical examination to confirm eligibility (e.g. to confirm that the knee problem is not due to causes other than knee OA, to check contra-indications to brace, e.g. condition of skin), and if eligible, for the purposes of stratification of randomisation (and subsequent subgroup analysis), the physiotherapist will determine, on clinical grounds, predominant compartmental involvement, and ask about the presence of knee instability (buckling).[87]

Plain X-rays of knees (if needed). To minimise unnecessary radiation exposure we will attempt to access and read knee X-rays taken in the last 24 months through PACS, the secure system used by the NHS to electronically store images like X-rays. However, we will obtain new knee X-rays for eligible participants who have no knee X-rays in the past 24 months, or whose knee X-rays are either unobtainable or unsuitable (e.g. poor quality images, lack necessary views). The availability of suitable X-rays will be checked on the PACS system by the clinic administrator. To determine the most severely affected compartment (and hence inform the selection of the appropriate brace), we require weight-bearing AP or PA view and lateral and skyline views of the knee that will be treated. Where these views are not available, new knee X-rays will be obtained according to the algorithm in Appendix 2. The maximum number of new plain X-ray views per participant is therefore three. All images will be taken in the radiology departments in each of the 4 NHS sites using NHS standard protocols. Knee X-rays (including those prior X-rays accessed through PACS) will be reported on as standard practice by a radiologist at each site. The treating physiotherapist will read the X-rays for the purpose of producing an overall judgement on the most severely affected compartment (medial tibiofemoral, lateral tibiofemoral, patellofemoral, no clear predominant compartment).

Eligible participants willing to participate in the trial will have an appointment booked to return to the PROP OA knee pain clinic 2 weeks later for their 'Treatment Visit'. This will allow sufficient time for X-rays to be read (or located if previously taken), reported, and X-ray and clinical findings combined by the physiotherapists to determine appropriate brace allocation (should the participant be allocated to BP+B). They will also be given a baseline questionnaire to complete at home and return at their 'Treatment Visit'. Participants deemed ineligible will be instructed to consult their GP (or physiotherapy service if recruited via physiotherapy) should their symptoms continue to be troublesome. GPs will be notified in writing if their patient has been recruited to the trial. Procedures for rapid consultation with a healthcare professional and referral to the participant's GP will be put in place for any participant presenting with a serious pathology such as fracture or malignancy. These procedures have been previously tested in the HTA SCOPIC trial by our team.[63] Participants who do not attend their Clinical Eligibility Assessment will be sent a letter asking them to re-contact the clinic and to book another appointment if they are still interested in participating in the trial.

7.2 Consent

At the visit for clinical eligibility assessment, trained physiotherapists will obtain participants' written informed consent to the assessment, which will be for judging eligibility and for clinical information needed should they be enrolled in the trial. Consent will also be sought for obtaining plain X-rays should these be required.
At the subsequent 'Treatment Visit', eligible participants will be invited to provide written informed consent to: participate in the trial; linkage to medical records; further contact regarding taking part in an interview. Baseline

questionnaires will then be checked, and participants randomised to receive either Best Primary Care (BP) or Best Primary Care plus Brace (BP+B), with treatment provided accordingly (as described in Section 4).

If potential participants do not attend their appointments at a PROP OA knee pain clinic (for Clinical Eligibility Assessment or Treatment), they will be contacted by the clinic administrator inviting them to arrange a new appointment. At all stages of the trial, any reason for non-participation will be recorded, if given.

7.3 The randomisation scheme

Using Keele CTU's computerised web-based randomisation service with random number generator, eligible participants recruited to the trial will be randomly assigned to receive either BP or BP+B, using a 1:1 allocation ratio and random permuted blocks. Randomisation will be stratified by PROP OA knee pain clinic site, predominant compartmental distribution of knee OA based on combination of clinical assessment and X-rays (patellofemoral, medial tibiofemoral, lateral tibiofemoral, no clear predominant compartmental involvement), and by presence of instability (buckling). Randomisation will be executed in real time within the 'Treatment Visit' by a clinic administrator. An off-site telephone emergency randomisation service will cover any temporary break in service. The randomisation code will be allocated only after the participant has been recruited into the trial, and after all baseline data collection is complete. The randomisation schedule will be password-protected to ensure that allocation remains concealed from all staff involved in the randomisation process. Thus our procedures ensure baseline data are collected prior to randomisation, that the allocation is concealed until after the participant has been recruited into the trial and until the moment of randomisation and that the person assigning participants to intervention groups (clinic administrator) has no involvement in the eligibility screen, consent or treatment processes. Clinic administrators will inform treating physiotherapists of the patient's allocation. The physiotherapist will then inform the patient and commence treatment accordingly.

7.4 Blinding

Within this trial it is impossible to blind participants or physiotherapists to treatment allocation. However, research staff involved in data collection and analyses (including the trial administrator overseeing collection of follow-up questionnaire data and minimal data collection over the telephone (see section 7.8 below); data entry administrator; and trial statisticians) will remain blind to treatment allocation until all data collection up to 12 month follow-up has been completed and the main intention-to-treat analyses of clinical effectiveness at 12 months performed. To ensure these research staff remain blind to treatment allocation, treatment arms in relevant databases will always be stored as a unique code and the key to unblind the treatments will only be known by the database designer and lead programmer. An evaluation of the success of the blinding procedures for minimum data collection over the telephone will be completed and a procedure for reporting incidents where blinding has been compromised will be in place.

7.5 Baseline data

The following forms will be completed prior to treatment:

- Informed Consent Form for 'confirmation of eligibility assessment' (including for obtaining plain X-rays of the knees if required)
- Eligibility Screening CRF
- Informed Consent Form for randomisation and intervention
- Participant baseline questionnaire.

The treating physiotherapist/trial administrator will check that all questions in the Baseline Questionnaire have been collected. Details of questionnaire content and outcome measures are given in section 3.5.

7.6 Trial assessments

Table 2. Schedule of enrolment, interventions and assessments

	Enrolment	**Random allocation**	**Post-randomisation**			
TIMEPOINT	***-8 to -0 weeks***	**0**	***2 wks***	***3m***	***6m***	***12m***
ENROLMENT:						
Telephone eligibility assessment	X					
Informed consent to assessment	X					
Clinical eligibility assessment	X					
Knee X-ray acquisition/reporting	X					
Knee X-ray reading		X				
Informed consent to randomisation, treatment, etc.		X				
Random allocation		X				
INTERVENTIONS:						
Best Practice Care (BP)		X				
Best Practice Care + Knee Brace (BP+B)		X				
ASSESSMENTS:						
Demographics	X					
Medical history and physical assessment	X					
Pain manikin]	X					
Frequent knee symptoms in last month	X					
KOOS-5[a]	X			X	X	X
KOOS Activities of Daily Living[b]	X			X	X	X
KOOS Pain[b]	X			X	X	X
KOOS Symptoms[b]	X			X	X	X
KOOS Sports/Recreation[b]	X			X	X	X
KOOS Quality of Life[b]	X			X	X	X
KOOS-4	X			X	X	X
Knee pain on weight-bearing activity (0-100 NRS)[b]	X			X	X	X

Intermittent & Constant Pain (ICOAP)	X			X	X	X
Knee buckling[c]	X			X	X	X
Physical activity (IPAQ-E)	X			X	X	X
Arthritis Self-Efficacy	X			X	X	X
HADS: Anxiety	X					
HADS: Depression	X					
PROMIS Social participation	X			X	X	X
Adverse events			X	X	X	X
Adherence to brace use[d]			X	X	X	X
Patient global rating of change[e]				X	X	X
OARSI-OMERACT responder criteria				X	X	X
Treatment acceptability				X		
EuroQol EQ-5D-5L	X				X	X
Healthcare resource use (NHS/private)	X			X	X	X
Out-of-pocket expenses	X				X	X
Time off work	X				X	X

§ Close-out at 12 months for analysis of clinical effectiveness; [a]Primary outcome; [b]Key secondary outcomes; [c] Single item used for stratified randomisation, multiple items used for outcome evaluation; [d] Obtained in part through: two-way SMS text messages at weeks 1,2,3,4,6,8,10,12,16,20,24,52; self-report via questionnaire at 3, 6 and 12-months, [redacted]; [e]Measure used only to classify OMERACT-OARSI responder

IPAQ-E International Physical Activity Questionnaire - Elderly; HADS Hospital Anxiety and Depression Scale; ICOAP Intermittent & Constant Osteoarthritis Pain; KOOS Knee Osteoarthritis Outcomes Score; NRS Numerical Rating Scale; OARSI-OMERACT Osteoarthritis Research Society International;

7.7 Long term follow-up assessments

To collect outcome data, participants will be sent a postal questionnaire at 3, 6, and 12 months post-randomisation. The questionnaire will include the primary outcome along with the secondary outcome measures described above in section 3.5. Participants will be asked to return the questionnaire to Keele CTU in a pre-paid addressed envelope that will be provided. Standard Keele CTU procedures will be followed to maximise follow-up, including post-card and questionnaire reminders following postal questionnaires at 3, 6 and 12 months. In addition, to encourage response and in recognition of the time given by participants, a £10 gift voucher will be sent to participants along with their 3, 6 and 12 month follow-up questionnaires.[109] At 6 months follow-up, the primary end point, non-responders will be approached for minimum data collection (MDC) 2 weeks after the reminder questionnaire is mailed. MDC is a shorter version of the self-report outcome questionnaire and will be used to collect the primary and limited secondary outcome measures (KOOS-5), global change scores, and EQ-5D-5L, along with date of birth and gender to ensure the data are provided by the intended participant. If no response to the MDC questionnaire, we will attempt to collect minimum data over the telephone by a trial administrator.

Data on self-reported adherence to brace use (in the BP+B group) will be collected by two-way SMS text messages at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 and 52 weeks.

7.8 Qualitative assessments – Nested studies

A theoretically informed qualitative study will be completed within the internal pilot and main trial, which builds on our previous qualitative work exploring acceptability of physiotherapy-led interventions for individuals with knee OA, and barriers and facilitators to non-pharmacological interventions (exercise and physical activity) in this population.[110-112]

Internal pilot qualitative study*:* Based on best practice guidance,[113] the aims of the qualitative study within the internal pilot are to investigate: a) the acceptability of trial procedures and interventions; b) adherence to interventions among participants (including barriers and enablers to brace use in individuals in BP+B); and c) barriers and enablers to successful delivery of interventions among trial physiotherapists. We will draw on Normalisation Process Theory (NPT)[114] to investigate the work required to deliver and adhere to bracing in the trial, and to understand treatment burden.[115] We will draw on the Theoretical Domains Framework (TDF)[74] to understand behavioural determinants of participant adherence to, and physiotherapist delivery of, interventions. We will undertake:

- Semi-structured one-to-one interviews with up to 20 trial participants (BP n=up to 10, BP+B n=up to 10) at 3-months follow-up
- Semi-structured one-to-one telephone interviews with physiotherapists who have delivered trial interventions within the internal pilot phase (n=up to 10).

The findings will be used to inform the decision to progress to the main trial, identify necessary changes to the trial processes or interventions for the main trial, and to inform on-going physiotherapy training and monitoring within the main trial.

Main trial qualitative study: To help explain the results of the trial in terms of the comparable clinical effectiveness of interventions, a qualitative study will be undertaken within the main trial to investigate contextual factors (i.e. factors external to the intervention, for example available resources, skills, and attitudes), and barriers and enablers to brace use in individuals with knee OA. Drawing on NPT[114,115] and the TDF[74], we will investigate patient and physiotherapy perspectives and will undertake:

One-to-one semi-structured interviews with up to 40 participants post intervention (at 6 months follow-up) (BP n=up to 20, BP+B n=up to 20). Interviews will be completed either over the telephone or face-to-face. Participants will be purposefully sampled from BP and BP+B (using data from trial questionnaires and SMS text messages) to ensure a diverse range of characteristics including age, gender, compartmental involvement, baseline pain severity, presence/absence of buckling, perceived overall improvement, and level of adherence. The interview topic guide will include open questions to explore participants' experiences of trial interventions, adherence to interventions (including barriers and enablers to brace adherence in BP+B), and impact of interventions on participants' symptoms, functioning and quality of life. Perceived harms and adverse events from interventions will also be explored. Data collection and analysis will be carried out iteratively so that emerging themes can be explored in subsequent interviews. Sampling will continue until no new themes emerge.

One-to-one semi-structured interviews with physiotherapists who have delivered trial interventions (n=up to 16). Interviews will be completed with physiotherapists over the telephone when they have finished treating their final trial participant. Physiotherapist interviews will provide insight into experiences of implementing, embedding, and integrating both BP and BP+B into NHS physiotherapy-led services. The acceptability of BP will be explored in addition to BP+B as this represents a novel way of delivering core NICE recommendations[10] within primary care settings. The topic guide will cover the appropriateness of the trial training programme, physiotherapists' views of their roles in the trial in terms of doing what they usually do (advice/education/exercise prescription) but in a single 20 minute treatment session, and in BP+B, the extra activity (basic reading and interpretation of X-rays, using a standardised clinical assessment to identify compartment of knee affected by OA, prescribing a brace and supporting the patient to use it, changing it where necessary), and using brief MI specifically to facilitate adherence to brace use.

All interviews completed within the internal pilot and main trial will be audio-recorded, transcribed verbatim, checked, and anonymised for analyses. Initially, each interview transcript will be read and re-read to identify and code discrete parts of the data that represent a particular concept. As analysis continues, using principles of

constant comparison,[116] data will be closely examined for similarities and differences, and groups of words or phrases representing the same concept will be grouped into themes. Emerging codes and themes will be discussed and agreed with members of the study team (including PPIE team members) on an ongoing basis and applied to the dataset with ongoing refinement as needed. Inductive analysis (described above) will precede deductive analysis and mapping of themes to TDF or NPT constructs.[74,114] This layered approach enables a rich interpretative analysis to be completed as emergent issues are identified ahead of making sense of data according to theoretical constructs.[114,117]

7.9 Withdrawal criteria

Participants may withdraw from the study at any time without giving reasons and without prejudicing any further treatment. Any information provided up to the point the participant withdraws will be used unless the participant asks for their data to be destroyed.

Early discontinuation of braces for any reason is not a reason for withdrawal from the study.

7.10 Storage and analysis of samples

All data will be stored and anonymised in line with Keele CTU Quality Management Systems.

[redacted]

7.11 End of trial

The trial end is at the point at which the trial database is locked. CRF data will have been received by the data management team at Keele CTU and any data queries will have been resolved. Copies of CRFs will remain at each participating site. The Chief Investigator will notify the REC of the end of the Trial within 90 days of trial completion.

8 STATISTICS AND DATA ANALYSIS

8.1 Sample size calculation

Bracing trials show standardised effect sizes (ES) for short-term improvements in knee pain and function of 0.33-0.56 and 0.22-0.48 respectively for tibiofemoral unloading braces[28] and 0.61 and 0.39 respectively for soft neoprene sleeve braces.[30] Our trial is powered to detect a between-group ES of 0.35 (small-to-medium effect) in primary outcome at 6 months with 2-sided 5% significance and 90% power, which, assuming a standard deviation of 23 as estimated from BEEP trial data,[67] equates to a minimum clinically important difference (MCID) of 8-points on the KOOS-5; an MCID value that aligns with published evidence for the tool.[118] We will randomise 434 patients to allow for 20% loss to follow-up at 6 months,[65-67] (target n at 6 months = 346; 173/arm). We have not inflated our sample size for therapist effects as each physiotherapist will be trained to deliver both interventions, however, the therapist will be included as a covariate in a sensitivity analysis of the treatment models to increase model power.[119]

8.2 Planned recruitment rate

Estimated recruitment rates: Based on data from our previous trials[63,67] we anticipate mailing 15,500 invitation letters, and that 20% will respond to express their interest (N = 3100). After eligibility screening by the trial administrator, we estimate that 25% (N=775) will be eligible and invited to attend the clinic and that 80% will attend (N=620). Further eligibility screening at the clinic could potentially reduce the pool of eligible participants by a further 30%, hence we aim to randomise 434 participants over 24 months, phasing in recruitment over the first 3 months (8, 12, and 15 patients respectively, then 19/month). Feasibility searches of

GP practices in West Midlands, Manchester, and Northumbria and data from the BEEP study[67] estimate that between 75 and 270 patients aged 45+ per 10,000 total registered population will consult with a relevant Read code in the previous 12-24 months (average = 166, which, given an average practice size of 7000, translates to 134 recruiting GP practices). This is a feasible recruitment goal as it would be overly conservative to base our recruitment estimates solely on the lower figure of 75 per 10,000 total registered population as we know all sites will be increasing the pool of potential patients by using the additional recruitment methods (screen of physiotherapy referrals and self-referral following awareness-raising), and by recruiting participants via prospective medical record review. In the event of any recruitment challenges, we also have the option to increase the time-frame of the retrospective search from 24 to 36 months (to allow for under-recording of prevalent cases) and to increase the number of GP practices to address any recruitment challenges.

8.3 Statistical analysis plan

A comprehensive analysis plan will be written to describe all pre-planned trial analysis. It will be kept as a separate document to this protocol and represents the *a priori* analysis plan. It will be written using standard operating procedures for Keele CTU and will be signed off by the TSC and DMC committees prior to lock down of the final dataset. Consequently, only a brief outline of the analysis plan is below.

8.3.1. Summary of baseline data and flow of patients

A CONSORT flow diagram will be produced to document the flow of participants through the study and will include reasons for study withdrawal if given. Any adverse events and protocol violations will be reported throughout the trial by treatment arm. Descriptive statistics will be used to describe the key baseline characteristics of participants included at each stage of recruitment and follow-up, and by treatment arm.

8.3.2. Primary outcome analysis

The primary outcome analysis will be on an intention-to-treat (ITT) basis and will compare the primary outcome (KOOS-5) at the primary endpoint (6 month follow-up) for BP+B versus BP after adjustment for pre-specified analysis covariates. Analysis of covariance (ANCOVA) will be used to generate treatment effect estimates that will be presented as mean differences with 95% confidence intervals**.**

8.3.3. Secondary outcome analysis

Secondary analysis will include the analysis of the primary outcome at 3 and 12 months (i.e. the secondary endpoints) and the secondary clinical effectiveness outcomes at 3, 6 and 12 months (as listed in Section 3.5). Analysis of covariance (ANCOVA) will be used for continuous outcome measures and logistic regression for dichotomous outcomes. Treatment effect estimates will be presented as mean differences or odds ratios (as appropriate) with 95% confidence intervals. To explore the need for an X-ray as part of the intervention, cross-tabulation and the kappa statistic will be used to test how accurate brace allocation would have been if based on clinical judgement alone, rather than on clinical and X-ray results combined. Treatment acceptability will be explored using numbers and percentages.

8.3.4. Subgroup analyses

Exploratory subgroup analyses will be performed (if numbers in each subgroup are sufficient for these analyses to be feasible) based on the presence of knee instability (buckling), predominant compartment involved, level of adherence, and anxiety/depression. This will be achieved by including an interaction term between treatment and the subgrouping variable of interest to the models described in section 8.3.2

8.3.5. Adjusted analysis

Covariates included in an adjusted analysis will be specified *a priori* in the analysis plan, but are likely to include the baseline in the outcome of interest and the stratification variables used in the randomisation process (i.e. site, knee instability (buckling) and predominant compartment involved), along with other key baseline variables of interest e.g. age and gender.

8.3.6. Interim analysis and criteria for the premature termination of the trial

No interim analysis will be undertaken during the trial to assess the clinical effectiveness of BP+B over BP. An internal pilot study however will be conducted (see section 10.6).

8.3.7. Subject population

All randomised participants will be included in the ITT analysis. Participants will be included in a per-protocol analysis if they meet pre-specified criteria for inclusion. Criteria will be pre-defined and are likely to be based around self-reported adherence to intervention. The definition for inclusion in the per-protocol analysis will be fully specified in the external analysis plan.

8.3.8. Procedure(s) to account for missing or spurious data

Multiple imputation will be used to account for missing data in the primary analysis. The variables to include in an imputation model will be pre-specified in the analysis plan. The random seed used in the imputation model will be recorded so that all imputation results can be reproduced and checked for analysis accuracy.

8.3.9. Other statistical considerations

Longitudinal mixed effects models will be used to evaluate the treatment effect at each single time-point and over time. These models will be used to check that results are consistent with those derived from the primary analysis. A statistically significant result will only be concluded if both analysis approaches show statistically significant findings.

8.4 Economic evaluation

8.4.1 Within trial economic evaluation

An economic evaluation will be undertaken alongside the trial to estimate the cost-effectiveness of BP+B versus BP in the management of knee OA. The analysis will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY) over 12 months follow-up, using patient level data on costs and outcomes from the trial. QALYs will be calculated from responses to the EQ-5D-5L questionnaire using the "area under the curve" approach. The crosswalk value set to obtain utility scores, in line with current NICE recommendations[120] and the more recent English value set will be used in a sensitivity analysis. The base-case analysis will be from a health care perspective, with an additional analysis from a societal perspective taking into account out of pocket cost and productivity losses. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be calculated for all trial participants. Analysis of productivity losses will use the human capital approach, and the self-reported days of absence will be multiplied by the respondent-specific wage rate. The human capital approach assumes that the value of lost work is equal to the amount of resources an individual would have been paid to do that work, and values productivity losses as a result of morbidity (or mortality) by measuring time lost from work and multiplying this with the gross wage of the person. As cost data is likely to have a skewed distribution, the nature of the distribution of costs will be explored, and if the data is not normally distributed, a non-parametric comparison of means (using bootstrapping) will be undertaken. Multiple imputation will be used to impute all missing values for the EQ-5D and total cost estimates for non-responders. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences (across the full range of clinical outcomes). Incremental cost-utility analysis will then be undertaken to estimate the incremental cost per QALY gained, adjusting for baseline covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

8.4.2 Model-based health economic analysis

Decision modelling will also be undertaken to extend the within-trial results beyond 12 months follow-up. The purpose of the model is to extrapolate costs and QALYs over a lifetime time horizon to calculate the long-term cost-effectiveness (cost per QALY) of the intervention, from an NHS perspective, with discounting of costs and outcomes at 3.5%. This is likely to be a Markov model which allows the representation of health states related to

the condition, recurrence of symptoms and new clinical events e.g. surgery. In addition to trial data, the model will be populated with data from existing literature on the natural history of the condition, risks associated with surgery and quality of life, and national data on all-cause mortality. The model will be subject to deterministic sensitivity analysis by changing individual parameter values and changing model assumptions, and probabilistic sensitivity analysis to simultaneously incorporate all parameter uncertainty. Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability the intervention is cost-effective at different cost/QALY thresholds. Conditional on additional funding available beyond the timeline of the current trial funding, model inputs can be updated with linked data on medium- to long-term outcomes from HES and NJR, and the model rerun to produce updated results.

9 DATA HANDLING

9.1 Data collection tools

Self-report questionnaires, SMS text messages and CRFs will form the basis of data collection.

9.2 Data handling and record keeping

Completed baseline self-report questionnaires will be checked and collected upon attendance at clinic ('Treatment visit') and forwarded to Keele CTU. Follow-up self-report questionnaires will be sent to the Keele CTU data management team in pre-paid envelopes provided to participants. Questionnaires will be date stamped on receipt at Keele CTU. Questionnaire data will then be logged as returned on a management database and the participants' responses entered into the trial database; the databases will be tested *a priori* for reliability. The study statistician will determine coding of questionnaire items, in accordance with standardised coding procedures of the Keele CTU, to facilitate data entry. Members of the research team will enter data and cross checks (a minimum of 1 in 10) will be carried out by other team members to ensure reliability and quality assessment of data entry.

The study is designed so that all participant personal data (e.g. names, addresses, interview audio files, interview transcripts prior to de-identification) are located on a database stored on a secure Keele University server accessed by two factor authentication, restricted to approved personnel. Furthermore, all data used for analysis will be kept separate from participant personal data to ensure anonymity to meet the necessary standards of the Keele CTU data security policy. Similarly, all hard copy information (e.g. signed consent forms, questionnaires) will be stored securely within the Keele CTU in accordance with Standard Operating Procedures (SOPs).

SMS text messages will operate using a third party text service provider which adheres to the Data Protection Act 2018 as well as the EC Directive "Private and Electronic Communications Regulations 2003". Communication between Keele CTU's secure server and the text message service provider is both encrypted and authenticated using a unique ID and password.

All protocol deviations are expected to be reported to Keele CTU as soon as the Investigator has become aware of the event. These will be reported accordingly to Keele University's SOPs

A Data Manager based at the Keele University CTU will oversee all responsibilities delegated to the CTU for data management and data entered to the trial database.

9.3 Access to Data

Direct access to trial-specific data only will be given to authorised representatives of the Sponsor to permit trial monitoring and audit.

9.4 Data Sharing Agreements

Keele CTU is committed to sharing access to our anonymised research data derived from our population, consultation, clinical, and RCT cohorts. Any requests for access to the data from anyone outside of Keele CTU

(e.g. collaboration, joint publication, data sharing requests from publishers) will follow Keele University's SOPs.

9.5 Archiving

Archiving will be completed as soon as possible after study closure, analysis and dissemination and will be in accordance with Keele CTU SOPs. At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 10 years after publication of the main findings and until the sponsor authorises destruction. Data held by Keele CTU will be archived in the designated Keele CTU secure archive facility and site data and documents will be archived by the participating sites in line with local protocols. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

10 MONITORING & AUDIT

10.1 Trial Management

The PROP OA trial is fully supported by Keele CTU, a UKCRC registered CTU. An experienced Trials Manager at Keele CTU will be responsible for day-to-day trial management, supported by a CTU Senior Trials Manager. The Trial Manager will support a Trial Coordinator at each of the collaborating academic sites. The trial will be sponsored by Keele University, and the Quality Assurance (QA) office will ensure QA in line with Keele SOPs. Keele CTU will provide trial services for: administration including invitation mailing and response management, data entry, follow-up administration and minimal data collection; IT to include database development, health informatics, data management, randomisation, SMS motivational prompts and SMS system; statistical design and analysis. Financial Management of the trial will be the responsibility of the lead applicant (Peat), supported by Keele's lead academic representative (Holden), the Senior Trials Manager, Keele CTU and the Institute of Primary Care & Health Sciences (iPCHS) Finance and Business Manager. Contracts will be developed and in place between the academic institutions and NHS sites, to clearly articulate roles and responsibilities.

The trial will be overseen by a Trial Management Group (TMG) chaired by the lead applicant (Peat) and consisting of representatives of all key groups involved in the design, operation and management of the trial. This group will meet monthly and will monitor progress along the planned timetable, discussing any issues as they arise and troubleshooting as required.

The lead NIHR Clinical Research Network (CRN) for the delivery of this trial will be West Midlands (WM). Their remit will involve the identification of potentially eligible participants and associated activities involved in site set-up and the recruitment of eligible participants. Lead contacts within the CRNs of Greater Manchester, North West Coast and North East & North Cumbria have also been made, to work with the clinical teams within their local participating NHS services. Our experience of working with these networks includes receiving valuable advice and feedback on the feasibility of planned recruitment methods, and on efficient ways of securing Network infrastructure and service support to secure timely delivery of research. In addition, we engage the resources of West Midlands CRN Physiotherapy Research Facilitators who also provide targeted support for partnering NHS services, site set up and participating physiotherapists. This collaborative approach has been successful in a number of previous trials supported by Keele CTU (e.g. HTA SCOPiC trial,[63] and the NIHR funded BEEP trial[67]. CRN representatives will attend relevant TMG meetings.

An independent Trial Steering Committee (TSC) that includes 2 patient representatives, and a Data Monitoring Committee (DMC) will be established to provide independent oversight of the trial. The TSC and DMC will meet initially at the start of the trial to approve the trial protocol and subsequently at regular intervals as agreed by the committee.

10.1.1 Trial Steering Committee (TSC) members

See under Key Trial Contacts.

10.1.2 Data Monitoring Committee (DMC) members

See under Key Trial Contacts. The DMC may request to review overall unblinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

10.2 Monitoring arrangements

The Keele CTU data management team will perform data quality checks of CRF data. Data queries will be entered to a log which will be sent to the trial manager, who will work with each site to resolve data queries in a timely fashion and provide further training as required. This, along with safety reports, will inform a risk-based approach towards assessing a need for any onsite monitoring visits. Trial monitoring reports will be reviewed by the Trial Management Group, Data Management Committee and Trial Steering Committee.

10.3 Safety Reporting

Collaborating centres should record events or concerns about the safety of subjects that arise as a result of the study, even if these events or concerns do not meet the definition of a Serious Adverse Event requiring notification to the regulatory authorities.

Adverse Events

The occurrence of adverse events considered to be related to the trial interventions for each intervention will be monitored and assessed using case report forms, contact with the trial team, physiotherapist report, and follow-up questionnaires. Expected adverse events from knee braces for knee OA include: swelling, blisters, and skin irritation. An expected adverse event from unaccustomed exercise and physical activity is temporary, mild muscle soreness. Physiotherapists delivering the interventions will advise participants about how to manage such symptoms.

Serious Adverse Events (SAE)

An SAE is an untoward event that:

(a) results in death;
(b) is life threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability/incapacity;
(e) consists of a congenital anomaly/birth defect; or
(f) is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant must be reported to the Research Ethics Committee (REC) where, in the opinion of the Chief Investigator, the event was *related*, i.e. it resulted from administration of any of the research procedures, and *unexpected*, i.e. the type of event is not an expected occurrence as a result of the intervention provided.

All SAEs considered to be potentially related to the trial procedures and occurring from the point when participants are registered on the trial will be notified to Keele CTU via telephone within 24 hours of the research staff at the site becoming aware of the event. Keele CTU will then provide the appropriate Case Report Form and inform the CI. The CRF must be completed and returned to Keele CTU (via fax or secure e-mail) within one week of receipt, and ideally within 24 hours. Clinicians will be asked to assess whether they considered the SAE was due to the trial procedures. Any follow-up information should be sent to Keele CTU as it is available. Events will be followed up until the event has been resolved or a final outcome has been reached. GPs will be asked in the letter that informs them of their patient's participation in the trial to report to Keele CTU any SAEs that they judge to be potentially related to PROP OA trial procedures.

All SAEs either confirmed or suspected to be related to the trial procedures will be reviewed by the Data Monitoring Committee and reported to the Trial Steering Committee.

Responsibilities for safety reporting

Principal Investigator (PI) at site

- Using medical judgement in assigning seriousness, causality.
- Ensuring that SAEs are recorded and reported to Keele CTU in line with requirements of the protocol.

Chief Investigator (CI)

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Assessing seriousness and causality where it has not been possible to obtain local clinical assessment.
- Review of all SAEs as described above.

Keele CTU

- Central data collection and verification of SAEs.
- Ensuring SAEs are reported to the trial steering committee and DMC.
- Preparing annual reports to the REC in collaboration with appropriate members of the TMG, and reports required by the sponsor.

10.4 Death notification form

All deaths occurring during the 6-month intervention period must be recorded on the Notification of Participant Death CRF.

10.5 Trial timeline

The trial will be delivered over 51 months between September 2018 and November 2022. See Gantt chart in **Appendix 1** for further details.

10.6 Internal pilot

An internal pilot will be completed to enable us to check our assumptions about the sample size and to test key trial processes and logistical issues including recruitment, intervention fidelity, adherence to brace use, follow-up and retention, and outcome measurement.

Objectives: Specific objectives of the internal pilot are to:

1) Check the numbers of eligible patients and rate of recruitment overall per month, per site per month, and per recruitment method (identification of General Practice consulters, screen of physiotherapy referrals, self-referral in the community following awareness raising)
2) Explore intervention fidelity and participant adherence to brace use
3) Check the trial retention rate

Methods: The internal pilot will last for 9 months, commencing from the start of recruitment (month 7 of the study timeline). All 4 sites will be included within the internal pilot, and the data collection methods used will be as per those of the full trial (as described above, and with an objective measure of brace adherence if deemed feasible within the pre-trial phase).

Data collection: Data from the following sources may be used within the internal pilot phase: telephone eligibility screening case report form; baseline, 3 month follow-up questionnaires (where available); text messaging (brace adherence data - BP+B only); physiotherapist case report forms; recruitment database; follow-up database; adverse event log; preliminary qualitative interviews with participants and physiotherapists.

Outcomes: Outcomes of interest for the internal pilot include:

1. Numbers of adults over 45 years with knee pain identified (per site; per recruitment method (including each awareness raising method employed); overall).
2. Number of individuals screened, number and reasons for ineligibility/exclusion/declining participation at telephone and clinical screening stage, and consent/randomisation rates (per site; per recruitment method; overall).
3. Retention and follow-up rates at 3 months (per site; overall).
4. Intervention fidelity measured by number of participants who have received the interventions per protocol, and reasons for any protocol non-adherence (including number of treatment sessions provided, content of treatment sessions, crossover, and off-protocol intervention (including co-interventions sought from participants)) (per site; overall).
5. Brace adherence in those randomised to receive BP+B, measured by self-report via SMS.
6. Relative distribution of most severely affected compartment (both arms) and brace type provided (BP+B only).
7. Patient and physiotherapist perceptions of acceptability of trial procedures and interventions.
8. Barriers and enablers to interventions among participants.
9. Barriers and enablers to successful delivery of interventions among trial physiotherapists.

Sample size: We anticipate that approximately 32 participants in BP+B will have 3 month data in the internal pilot, hence we can estimate the proportion of patients adhering to braces with at least 95% confidence and a 20% margin of error, assuming adherence and fidelity rate of 50% as a worst case scenario for desired precision.[121] As other important estimates of recruitment and follow-up will be derived from participants with data in both treatment arms, their estimated precision in the internal pilot study will be greater than that for adherence and intervention fidelity (which is estimated from the BP+B treatment arm only).

Progression criteria: A success criteria traffic-light system relating to the internal pilot trial objectives will be used to inform whether we 'stop' 'proceed' or 'proceed but with protocol amendments' to the full trial.[121] These criteria are shown in Table 3 below and will be finalised with the Trial Steering Committee (TSC) and funder in the pre-trial phase.[121] We recognise the arbitrary nature of these cut-offs, however having them in place will allow us to identify any issues that are addressable in going forward to a main trial.[121] Qualitative findings will also be available to the TMG, TSC and funder at the time of decision making regarding progression of the pilot trial. These will be used to help understand the findings of the internal pilot and will be used to help make the final decision as to whether we should stop, proceed, or proceed but with protocol amendments to the full trial.

Table 3. Progression criteria for internal pilot

	Proceed to main trial	**Proceed to main trial with protocol amendments**	**Do not proceed to main trial**
Recruitment ***In months 7-9 of recruitment:***	Site has recruited over 4 participants per month; recruited 19 participants per month overall	Site has recruited 3-4 participants per month; recruited 12-18 participants per month overall	Site has recruited fewer than 3 participants per month; recruited fewer than 12 participants per month overall
Intervention fidelity	Interventions delivered per protocol for at least 75% of participants (per site; overall)	Interventions delivered per protocol for 45-75% of participants (per site; overall)	Interventions delivered per protocol for fewer than 45% of participants (per site; overall)
Adherence to brace use (BP+B only)	At least 75% of participants reporting minimal level of brace adherence at 3 months* (per site; overall)	Between 45-74% of participants reporting minimal level of brace adherence at 3 months* (per site; overall)	Fewer than 45% of participants reporting minimal level of brace adherence at 3 months* (per site; overall)
Retention and follow-up at 3 months	At least 75% retention and follow-up at 3 months (per site; overall)	Between 50-74% retention and follow-up at 3 months (per site; overall)	Fewer than 50% retention and follow-up at 3 months (per site; overall)

*Minimal level of brace adherence: wearing the brace for 1 hour on two or more days per week

11 ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial has been designed, and will be run, in accordance with the Principles of GCP. The trial involves the investigation of interventions in practice. All braces used in the trial are CE marked mass-product (not custom-made) medical devices being used for their intended purpose.
We do not anticipate any major ethical concerns with this trial. All patients will receive at least Best Primary Care that aligns with best evidence recommendations from NICE.[10] In addition, some participants will also be randomised to receive a knee brace already used within clinical care in the NHS. All interventions are deemed safe, with few and minor expected adverse events (for example skin irritation from knee braces, muscle soreness from exercise). Participants in both treatment arms will be able to consult for health care in addition to the care they receive within the PROP OA trial, and this will be recorded and analysed. Participation in the trial may involve exposure to ionising radiation in the form of plain radiography to obtain knee X-rays at baseline. Imaging procedures will be compliant with the Ionising Radiation (Medical Exposure) Regulations 2000 and the amendments in 2006 and 2011. The imaging protocol will be reviewed prior to REC submission by a Medical Physics Expert and Clinical Radiation Expert.

The trial requires the recruitment of patients identified within the NHS to an individually randomised trial involving the collection of primary patient-based data. Health Research Authority (HRA) approvals will be applied for and sought before the study commences. HRA Approval is the process for the NHS in England that brings together the assessment of governance and legal compliance, with independent Research Ethics Committee opinion provided through the UK Health Departments' Research Ethics Service.

Potentially eligible patients will receive information about the trial and will have time to consider this prior to undertaking telephone screening, and prior to attending the PROP OA knee pain clinic, where they will be able to discuss participating in the trial with a PROP OA trained physiotherapist, prior to providing written informed consent. Consent will also be sought for linkage to Hospital Episode Statistics, the NJR and medical record review.

[redacted]

All data collected during the course of the trial will be handled and stored in line with Keele CTU's Data Security procedures and SOPs, which are in accordance with the Data Protection Act 2018, other relevant regulations and GCP guidelines. We will anonymise and archive the data for 20 years on a secure server at Keele University. Nicholls will be the data custodian. We will make the data accessible to other researchers, in line with Keele CTU procedures.

11.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and patient self-report questionnaires.

- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed by NHS R&D departments before they can be implemented in practice at sites).
- All correspondence with the REC will be retained in the Sponsor Trial Master File/local Investigator Site File.

- An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

11.2 Peer review

The study has been funded by the NIHR HTA Programme through open competition and hence has undergone external peer review by appropriate patient and healthcare professional representatives.

11.3 Public and Patient Involvement

Two patient representatives are members of the trial team and helped on the grant application and have actively contributed to revising the trial protocol following Clinical Advisory Group and Panel feedback. A 3-hour workshop was convened with 5 patient representatives with knee OA to discuss recruitment, participant flow, interventions (including trying on/ discussing various patellofemoral, tibiofemoral unloading, and neutral stabilising knee braces), outcome measures and dissemination. Comments about the trial were also invited from the general public via the interactive VoiceNorth discussion forum and specific feedback from 9 VoiceNorth members (http://www.voicenorth.org/). As a result the following changes were made: 1. Self-referral recruitment campaign broadened; 2. Primary outcome changed to composite score including pain and function ("pain is what you start with, if pain improves then function improves"); anxiety, depression and participation included as secondary outcomes; 3. Reasons for brace non-adherence to inform decision to progress from internal pilot.

To further refine the design of the trial a second PPIE workshop was convened in the pre-trial phase to finalise the adherence-enhancing SMS intervention (e.g. content of text messages). In addition, the internal pilot findings will be discussed with the Research Institute's Research User Group (RUG) members, who will contribute to proposed amendments that may needed to progress to the main trial. To ensure ongoing oversight and input, our PPIE study members will attend TMG meetings, and assist in the interpretation of qualitative findings. Two members of our RUG will also sit on the TSC. Finally, our PPIE study members will play an important role in developing key messages about trial findings. This will benefit our dissemination strategy and ensure findings are translated into statements that are easily understandable. We have an established track record in publishing our PPIE related work.[122-124] Joint publications and conference presentations with patients have also previously been undertaken in order to involve patients in the dissemination of research that they have been involved with and also share good practice.[125-127]

By active, ongoing PPIE involvement, our research will be more relevant to patients' needs, and conducted in a more patient-friendly manner, thus supporting trial recruitment and adherence. All PPIE activity will follow our Research Institute's written framework for PPIE involvement that is based on INVOLVE,[128] and will be supported by our PPIE Research Administrator and user support worker. This includes feedback being provided after meetings on what was discussed and how the discussions feed into the ongoing trial. All patient representatives will receive a trial glossary and will have access to training resources (e.g. contributing assertively to meetings, INVOLVE resources). We offer payment for PPIE activity according to INVOLVE guidelines.

To help inform the development of the PROP OA trial protocol we have also formed, and convened two workshops with, a CAG consisting of clinicians (including physiotherapists) currently involved in the delivery of braces for patients with knee OA [redacted]. Our PPIE co-applicants actively participated in these workshops. Following the workshops the following changes were made: (1) X-ray added to help determine

clinical subgroup; (2) holistic assessment to be added when making final decision about which brace to provide, to also take into account current and desired level of physical activity, ability to don/doff brace, willingness to wear the brace type, and immediate symptom response when the brace is tried on and tested in clinic; (3) enabling some patient choice in brace options for brace types where there are likely to be the greatest challenges with fit and appearance; (4) simplification of exercise programme; (5) refinement of eligibility criteria. Members of the CAG have provided, and will continue to provide, ongoing advice. A further CAG workshop will be convened in the pre-trial phase to finalise the content of the physiotherapist training programme.

11.4 Regulatory Compliance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in research studies, the UK Policy Framework for Health and Social Care Research. Keele CTU have a quality management system in place containing standard operating procedures which will be adhered to in the conduct of the study. Studies run by Keele CTU may be subject to an audit by Keele University as the Sponsor for quality assurance.

11.5 Protocol compliance

Non-compliance may be identified through any study activity but in particular through the use of central monitoring procedures such as consent form review or data management, site visits and self-reporting by the study site or participants. Deviations from protocols and GCP may occur in research studies. The majority of these instances are technical non-compliances that do not result in harm to the study participants, do not compromise data integrity, or significantly affect the scientific value of the reported results of the study. These technical deviations will be documented, and appropriate corrective and preventative actions will be taken by the research team with responsibility being taken by the CI and where needed with agreement from the TSC.

11.6 Notification of Serious Breaches to GCP and/or the protocol

Participating sites are expected to notify Keele CTU as soon as they become aware of a serious breach. A "serious breach" is a breach which is likely to affect to a significant degree –

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

These will be reported accordingly to Keele University's SOPs.

11.7 Data protection and patient confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and managed electronically by Keele University through Keele CTU. Keele CTU complies with data protection regulations:

- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- Consent from participants for access to their healthcare records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research
- All data collection forms that are transferred to and from Keele CTU will be coded with a trial number and will include up to three further participant identifiers: the participants' gender, initials and date of birth
- Where anonymisation of documentation is required, participating centres are responsible for ensuring only the instructed identifiers are present before sending to Keele CTU

All data will be housed in the CTU infrastructure, which is a secure virtual network requiring two factor authentication in order to access the data stored within. Roles and permissions are applied to users within the network as well as within an application to restrict what data a user can access and operations they can perform. All research staff/CTU operational staff involved in this study adhere to robust data security procedures and have explicit duties of confidentiality. These practices are written into their employment contracts and are equivalent to the duty placed on NHS staff.

If a participant withdraws consent from further trial intervention and/or further collection of data their data will remain on file and will be included in the final study analysis.

11.8 Financial and other competing interests for the chief investigator, associate investigator, PIs at each site and committee members for the overall trial management

George Peat, Melanie Holden, David Felson, Michael Callaghan, and Fraser Birrell have no financial or other competing interests to declare. The members of the TSC also have no financial or other competing interests to declare.

11.9 Indemnity

The trial is sponsored by Keele University and therefore Keele University will be liable for negligent harm caused by the design of the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a trial, and the NHS organisation remains liable for clinical negligence and other negligent harm to patients under this duty of care.

Agreements between the sponsor and participating NHS organisations detailing trial conduct and the responsibilities to be honoured by each party will be fully executed before the trial can start at the local NHS Trust.

11.10 Post trial care

Participants allocated to the BP+B intervention will be allowed to keep their brace after the end of the trial intervention period.

12 DISSEMINATION POLICY

Our main findings on the clinical and cost-effectiveness of adding knee bracing to Best Primary Care will have important implications for patients and the NHS. To ensure that the outputs from the research inform clinical practice, the following dissemination strategy has been developed based on NIHR 'Push the Pace' guidance, draws on our extensive existing communication channels and networks, and is led by KD, a NICE Fellow, and lead of the Impact Accelerator Unit within Arthritis Research UK Primary Care Centre at Keele University. The five key audiences for this research are:

a) patients with knee pain/OA and the wider public;
b) healthcare professionals;
c) CCGs and commissioning organisations;
d) external statutory bodies, patient groups and charities;
e) academia.

To maximise its effectiveness, our dissemination activities will be co-ordinated in time, use multiple channels to reach multiple audiences, and where possible include face to face, in-depth interaction.

Our strategies include:

- Written feedback to trial participants and participating GP practices **(a,b)**
- Feedback via all communication strategies adopted within the recruitment awareness raising campaign (e.g. newspaper articles and interviews on local radio, press release, posters in community and health care settings) **(a,b,c)**
  Interactive workshops in the West Midlands, Greater Manchester and Northumbria on the role of knee bracing for knee OA **(a,b,c)**
- Links with key local, national and international organisations including the West Midlands Academic Health Science Network, West Midlands Collaborations for Leadership in Applied Health Research and Care (CLAHRC), NICE, Arthritis Care, Arthritis Research UK, European League Against Rheumatism (EULAR), and Osteoarthritis Research Society International (OARSI), to contribute to and capitalise on their networks. Felson is on the OARSI working group executive committee that writes papers for government policy **(a,b,c,d,e)**

- Use of electronic media including a trial website, institutional websites (e.g. ROAM), Blogs (e.g. VoiceNorth), social media including Twitter, webinar and Youtube video **(a,b,c,d,e)**
- Publications including full report, executive summary and plain English summary, peer-reviewed journals, and local NHS and research newsletters **(a,b,c,d,e)**
- High-profile national and international conferences - Society for Academic Primary Care, Chartered Society of Physiotherapy, NHS Evidence, OARSI, EULAR, American College of Rheumatology **(b,c,d,e)**

The expected output of our research are:

- An understanding of the clinical and cost-effectiveness of adding knee bracing to Best Primary Care for knee OA
- An understanding of the barriers and facilitators to knee brace use in individuals with knee OA
- A primary care-based, physiotherapy-led service model for the delivery of knee braces for knee OA
- An adherence enhancing intervention for knee braces
- A training programme for physiotherapists on the provision of knee braces for knee OA
- Written materials on: i) Best Primary Care for knee OA, ii) knee brace care and maintenance; and a diary for monitoring knee brace use
- Lay summaries of study results in various formats, including summary sheets, newspaper and magazine reports, video clips, blogs and Tweets
- Publications in high impact academic journals and research summaries for professional leaflets, magazines and journals
- A published full and complete account of the research in the NIHR HTA Journal

This RCT will provide definitive evidence of the comparative clinical and cost effectiveness of adding knee brace (matched to patients' clinical and radiographic presentation and with adherence support) to Best Primary Care (BP+B) compared to Best Primary Care alone (BP), in adults with symptomatic knee OA. This will inform patients, clinicians and commissioners. Our cost effectiveness analysis will be important to NICE and commissioners developing new clinical recommendations, services and evidence-based pathways of care. The research team is well placed to ensure that outputs from this trial reach national and international audiences, and are incorporated into routine clinical practice. In addition, trial data will be archived and stored at Keele CTU for future access and sharing. For example, by using similar outcomes to previous trials, future meta-analysis, and individual participant data meta-analysis are also possible, including via the OA trial bank, (www.oatrialbank.com), an initiative established in 2010 to collect and analyse IPD of published RCTs in OA.[68,69]

Authorship eligibility guidelines and any intended use of professional writers

Authorship will be available to those who fulfil the International Committee of Medical Journal Editors (ICMJE) criteria (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and in accordance with the requirements and guidance for authors from the NIHR Journals Library (https://www.journalslibrary.nihr.ac.uk/information-for-authors/).

Staff heavily involved in the practicalities of study operationalisation and delivery, including dedicated study co-ordinators, will be considered for co-authorship of protocol papers on the condition they can contribute to critical revision of drafts, approve the final version, and be accountable for the content.

There is no intention to use professional writers.

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14. APPENDICES

14.1 Appendix 1 - Gantt chart

14.2 Appendix 2 - Algorithm for requesting new X-ray views

14.1 Appendix 1 - Gantt chart

	2018					2019													2020													2021													2022										
Calendar Months		S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N
Project Months	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
Management, Oversight & Advisory Meetings																																																				
Trial Management Group																																																				
TSC / DMC																																																				
Clinical Advisory Group																																																			
Research User Group																																																			
Development and Set-Up																																																			
Staff appointments																																																			
Finalise trial protocol																																																			
Trial registration																																																			
Develop study documentation																																																			
Finalise detailed operations procedures																																																			
Obtain HRA (REC/R&D) approval																																																			
Database design, development, testing																																																			
GP practice engagement																																																			
Clinical site liaison and set-up																																																			
Training and Audit																																																			
Development of training materials																																																			
Workshops and training for clinicians†																																																			
Audit of study procedures																																																			
Recruitment, Treatments, Follow-up, Interviews																																																			
Awareness raising campaign																																																			
Recruitment (all centres)																														‡																						
Treatments delivered to participants																																																			
Follow-up																																																			
Interviews with patients																																																			
Interviews with physiotherapists																																																			
Analysis and Write-up																																																			
Qualitative analyses																																																			
Data cleaning																																																			
Main trial data analysis																																																			
Health economic analysis/modelling																																																			
Final report to HTA																																																			
Peer-reviewed journal papers																																																			
Conference presentations																																																			
Other dissemination of trial findings																																																			
Medical Record and NJR Linkage																																																			
NJR/HQIP permissions for NJR linkage																																																			

Black shading = internal pilot

†Ongoing email and telephone support from bracing and brief MI experts, visits and observations offered if required.

‡Last invitations mailed out

14.2. Appendix 2 - Algorithm for requesting new X-ray views