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PAKA (Perioperative Analgesia for Knee Arthroplasty) Protocol

Protocol for a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus single agent femoral nerve blockade as analgesia for total knee arthroplasty

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Title

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Protocol for a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus single agent femoral nerve blockade as analgesia for total knee arthroplasty.

Registration

The study has been registered with the current controlled trials database under reference number ISRCTN 60611146 and has the following EUDRACT Number 2013-002439-10 (protocol code number PAKA-33601-AS117013)

Roles and Responsibilities

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Abstract

Introduction:

Total knee arthroplasty (TKA) surgery generates substantial postoperative pain. Recently, the use of peri-operative injections around the knee containing analgesics, such as local anaesthetics, opiates and non-steroidal anti-inflammatory drugs has increased in popularity to manage post-operative pain. Theoretical advantages include reduced requirements for analgesia and earlier mobilisation. We propose a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus single agent femoral nerve anaesthetic blockade (standard treatment) as analgesia for TKA. The aim of the trial is to determine, in patients undergoing TKA (population), if there is a difference in patient reported pain scores on the Visual Analogue Score (VAS) (outcome) prior to physiotherapy on day one post-operatively between treatment groups.

Methods and analysis:

All patients undergoing a primary unilateral TKA at University Hospitals Coventry and Warwickshire Hospitals will be assessed for eligibility. A total of 264 patients will provide 90% power to detect a difference of 12mm on the VAS on day one post-operatively at the 5% level. The trial will use a 1:1 randomisation sequence, stratified by mode of anaesthetic. The primary outcome measure will be the VAS for pain prior to physiotherapy on day one. Secondary outcome measures will include VAS on day two, total use of "as required" analgesia in 48 hours, ordinal pain scores for the first 40

minutes after surgery, independent routine functional physiotherapist assessment on day one and two. Oxford knee Scores (OKS), EuroQol (EQ-5D) and Douleur Neuropathic Pain Scores (DN2) will be recorded at baseline, 6 weeks and 12 months. All complications will be recorded up to 12 months. The main analysis will investigate differences in VAS on day one between the two treatment groups on an intention-to-treat basis. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05.

Ethics and dissemination: NRES Committee West Midlands, 23rd September 2013 (ref: 13/WM/0316). The results of the trial will be disseminated via peer-reviewed publications and presentations at relevant conferences.

Strength and limitations

This trial will assess the clinical effectiveness of multimodal peri-articular anaesthesia infiltration versus single agent femoral nerve blockade as analgesia for total knee arthroplasty. Methodological qualities of the trial include: a pragmatic design to facilitate implementation within routine clinical practice, an optimised protocol to reduce risk of bias, appropriate sample size calculation and a planned intention-to-treat analysis. The main limitations of this study will be a lack of blinding amongst clinicians delivering the intervention and its single centre design.

Introduction

Total knee arthroplasty (TKA) is the commonest joint replacement, with over 82,000 procedures performed annually in the National Health Service (NHS).[1] Demand is growing and this, combined with an ageing population, the frequency of TKA and its burden on the NHS increases year on year. During the last decade there has been increased interest in optimal peri-operative care to enhance recovery following TKA. Improvement of analgesia; reduction of surgical stress responses and organ dysfunctions; including nausea, vomiting and ileus; early mobilisation; and oral nutrition have all been examined. Measures to try and improve pain management have been developed including multimodal regimes which theoretically allow functional rehabilitation to be initiated more rapidly postoperatively. TKA generates substantial amounts of postoperative pain, which effects range of movement and ability to mobilise. Good pain relief with minimal physiological disturbance is important for postoperative knee rehabilitation.[2-4] Epidural analgesia is very effective in pain control but is associated with side effects such as pruritus, urinary retention and motor block.[2] Epidural analgesia can also occasionally lead to serious complications such as spinal cord ischemia, vertebral canal haematoma, vertebral canal abscess, infective meningitis, nerve and spinal cord injury, wrong route administration and cardiovascular collapse.[5]

The use of opioid drugs, administered by means of either patient-controlled analgesia or other methods, is another effective method of postoperative pain relief but is often associated with systemic side effects, including nausea and vomiting, respiratory depression, drowsiness, pruritus, reduced gut mobility, and urinary retention.[6] Drowsiness in particular may delay the patient's post-operative mobilisation. Femoral nerve block, as a single peri-operative infiltration or via an indwelling catheter, has been shown to improve post-operative pain control and reduce the use of systemic analgesics and is currently the standard care for peri-operative analgesia.[7] The key advantage of the technique is that it avoids the systemic effects associated with both epidural and opioid analgesics. However, it may be associated with complications such as vascular puncture, nerve damage, infection and diminished muscle control.[8] The inhibition of the quadriceps muscle group can delay post-operative mobilisation.[9] Since the posterior capsule of the knee joint is innervated by the branches of the sciatic nerve rather than the femoral, femoral nerve blockade may also result in incomplete pain relief.

Recently the use of intra-operative, peri-articular infiltration of multimodal analgesics has gained in popularity. Peri-articular infiltration has the advantage of delivering drugs directly to the sources of

pain, thereby avoiding systemic side effects.[10]. The concept of multimodal analgesia refers to the simultaneous administration of multiple anaesthetic agents, such as local anaesthetics, opiates and non-steroids anti-inflammatory drugs. To produce optimal pain relief combined with the lowest incidence of side effects, a multimodal pain therapy is essential.[5] This technique of analgesia was developed specifically to avoid sedation and facilitate rapid physiological recovery after lower limb arthroplasty in order to enable early mobilisation and discharge.[9-13] In contrast to femoral nerve blockade, peri-articular infiltration does not inhibit quadriceps function and also reaches the posterior capsule of the knee joint. Published studies suggest that peri-articular infiltration may reduce requirements for post-operative analgesia, lead to earlier mobilisation and discharge from hospital. However, the number of published randomised controlled trials involving TKA is small and all are underpowered and lack statistical rigour. An initial pilot study has already been completed in order to help plan and design a full trial with the following null hypothesis[14]:

Post-operative pain following primary TKA does not differ between multimodal peri-articular knee infiltration with Levobupivicaine 150mg, Morphine 10mg and Ketorolac 30mg diluted in 0.9% saline to make a volume 100ml (0.5ml 1:1000 adrenaline) and the single agent femoral nerve blockade (the current standard).

Objectives

The primary objective of this full trial is to quantify and draw inferences on the efficacy between treatment groups based on observed differences as shown by a validated, patient reported 100mm visual analogue pain score, pre-physiotherapy on the first post-operative day, collected by an independent physiotherapist. This is the most important outcome as pain at the time when the patient is first starting to walk and use their new knee replacement will determine the ability of the patient to mobilise. Early mobilisation is associated with improved functional outcomes and a reduced risk of complications.[15]

The secondary objectives of the study are to quantify and draw inferences on the efficacy of the treatment groups based on observed differences as shown by:

1. Visual analogue scale after physiotherapy on the first post-operative day and before and after physiotherapy on the second post-operative day.
2. The total use of “as required” analgesia in the first 48 hours after the operation.
3. Ordinal pain score (routinely collected up to 40minutes after surgery.
4. Independent routine functional physiotherapist assessment on day one and two postoperatively assessing: straight leg raise, knee range of movement, Timed Up and Go, bed transfers and distance mobilised.
5. Oxford Knee Score (OKS) collected pre-operatively and 6 weeks post-operatively.
6. EuroQol (EQ-5D–5L) Score collected pre-operatively and 6 weeks post-operatively.
7. DN2 Douleur Neuropathic Pain (DN2/Seven Item DN4) Score, collected pre-operatively and 6 weeks and 12 months post-operatively.[16 17]

Methods and analysis

The protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[18] Approval was obtained on the 23rd September 2013 under reference number 13/WM/0316. This study is jointly sponsored by the University of Warwick and University Hospitals Coventry & Warwickshire NHS Trust. The trial will be carried out in accordance with the Medicines for Human use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP); all collaborators will be trained in GCP, and in accordance with this protocol. This trial will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.

All patients undergoing an elective primary unilateral TKA under the care of an orthopaedic consultant at University Hospitals Coventry & Warwickshire NHS Trust are potentially eligible for entry to the trial. However, patients with any of the following will not be eligible:

1. Concomitant medical or psychiatric problems which, in the opinion of the Investigator, would prevent completion of treatment or follow-up.
2. Pre-operative history of neurological abnormality in the ipsilateral leg e.g. history of stoke, neurogenic pain or previous nerve pain.
3. Specific contraindication to the analgesic agents used:
   Morphine
   i. Hypersensitivity reaction
   Ketorolac
   i. Active or previous peptic ulcer
   ii. History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy
   iii. Haemorrhagic diatheses, including coagulation disorders
   iv. Hypersensitivity to ketorolac trometamol or other NSAIDs
   v. Moderate or severe renal impairment (serum creatinine > 160 micromol/l)
   Levobupivacaine
   i. Known hypersensitivity to levobupivacaine, local anaesthetics of the amide type or any of the excipients
   ii. Uncontrolled angina
   iii. 2nd or 3rd degree heart block
4. Participation in a clinical trial of an investigational medicinal product in the last 90 days.
5. Previous entry in the present trial.
6. Evidence that the patient would be unable to adhere to trial procedures.

Patients fulfilling the eligibility criteria will be identified by consultants and research associates in outpatient clinics. Patients already on the waiting list (as identified via hospital operative planning software, Opera) for a unilateral TKA may be contacted during their pre-operative assessment at the hospital, which normally occurs a few weeks before surgery. All appropriate patients will be approached as per ICH-GCP guidelines. Patients will only be given Letters of Invitation if, in the opinion of the recruiter, there has been an adequate verbal introduction to the trial. Patients will be given adequate time to consider their participation. This process will ensure that patients have sufficient time to consider the information given to them prior to being asked to provide informed consent to participate in the trial. Signed and dated informed consent will be obtained before conducting any procedure for the trial by trained personnel. In the event that any further information becomes available which may influence the patient's willingness to continue in the trial, the trial team will contact the participant. The participant's General Practitioner (GP) will be informed by letter that the patient is taking/has taken part in this clinical trial. A participant may deny the research team permission to inform the GP of their trial involvement by not initialling the appropriate box on the consent form. Pre-randomisation eligibility checks will be carried out to ensure that a patient fit the eligibility criteria and is not randomised in error. Inclusion of a patient in the trial will be flagged on their clinical notes by means of a trial sticker.

Randomisation

Allocation of trial treatments will be provided through a distal randomisation service that use a computer generated randomisation sequence. To ensure allocation concealment the mechanism of contact being used is via a telephone and has a stringent procedure to ensure enrolment before randomisation. Patients will be stratified by anaesthetic type - general or spinal block - before

sampling is performed, and randomised into one of two groups: the femoral nerve block group or the peri-articular injection group.

Sample Size

The primary outcome measure for this study is pain on day one post-operatively, assessed using a 100mm visual analogue scale (VAS). Pilot data (n=46) was used in a power analysis to estimate the sample size required for a two-arm parallel group RCT. Based on the available literature, a change in the VAS of 12 mm (95% CI 9mm-15mm) is clinically meaningful, thus these calculations assume the minimum clinical important difference (MCID) to be approximately 12mm.[19] The observed standard deviation from the pilot study was 30mm, giving a standardised effect size (MCID/SD) of 0.4, a moderate value, and of the appropriate order of magnitude for a pragmatic study of this type. Hence to power a trial to test the null hypothesis of equality of the treatments, assuming approximate normality for the VAS, would require 132 patients in each treatment arm or 264 in total - assuming 90% power, 5% significance, a standard deviation of 3cm and an MCID of 12mm. Given that the majority of data collection will occur during participant hospital stay, with the exception of the patient reported outcome measures, we anticipate loss of follow-up data will be minimal (<5%). The sample size for this trial corresponds to effects observed in previous similar studies.[19 20] These studies demonstrated effects on a 100mm visual analogue scale (VAS: our primary outcome measure) and on participant consumption of "as required" analgesia with 20-25 patients per experimental group.

Recent audit within the department indicated there are approximately 50 elective primary unilateral total knee replacements carried out per month, of whom over half would be eligible for this trial. Although not all patients will want to take part, our previous experience in trials of perioperative adjuncts to surgery has shown high levels of patient recruitment (80-100%) with only 7% declining the pilot study. Therefore we believe 11 patients per month to be a realistic recruitment figure. At this rate the entire study sample can be recruited within 24 months. However, if recruitment rate is not as high as anticipated, a sample size of 200 patients will still be adequate to identify any difference between groups with 80% power.

Participants may withdraw from the trial treatment and/or the whole trial at any time without prejudice. Unless a participant explicitly withdraws their consent they should be followed-up and data collected as per the protocol until the end of the trial.

Should a participant withdraw from the trial they would continue to be treated as per normal routine postoperative management, follow-up and clinical practice. The data collected up until the point of withdrawal would be used for analysis at the end of the trial. Subjects may be withdrawn from the trial at the discretion of the Investigator and/or the Trials Steering Committee due to safety concerns.

Blinding

Patients will be blind to the intervention to which they are allocated, as femoral nerve blocks will be done after sedation and or anaesthetic. All interventions will be conducted within a sterile zone with drapes which will physically prevent patients seeing which intervention they receive. Due to the nature of the study it is not possible for the surgeon and anaesthetist delivering the interventions to be blinded to the treatment options. Outcome data will be collected by a research associate and an independent clinical physiotherapist who are blinded to the treatment allocation. Furthermore, the trial statistician will be blinded to the treatment allocations throughout.

Interventions

In this pragmatic trial, patients will undergo routine elective primary unilateral TKA using the standard technique of the anaesthetist and the operating surgeon. In addition, the patient will receive one of the following peri-operative analgesic interventions:

1. Femoral Nerve Block

Under aseptic conditions, the femoral artery will be palpated immediately below the inguinal ligament and nerve stimulation and or ultrasound will be used to identify the femoral nerve just lateral to the artery. Once the femoral nerve has been identified the block may be performed in the routine manner (15, 16) using 30 ml (75mg) of levobupivacaine hydrochloride 0.25%.

2. Intraoperative Peri-articular Injection

The peri-articular infiltration of multi-modal agents will involve the preparation of two 50ml syringes each containing 30ml (75mg) of levobupivacaine hydrochloride 0.25% injection, 0.5ml (5mg) morphine sulphate injection, 0.5ml (15mg) ketorolac trometamol injection and 0.25ml of 1:1000 adrenaline then diluted with 0.9% saline to make a mixture containing a total volume of 50ml. Adrenaline is added to the mixture to reduce blood loss after the operation. Each syringe will be prepared for immediate use and not stored. 50ml of the mixture will be injected into the posterior, medical and lateral soft-tissues just prior to implantation of the TKR components. Care will be taken to avoid excessive infiltration in the area of the common peroneal nerve. Then, whilst the cement is curing, the anterior soft-tissue including the quadriceps mechanism, the retinacular tissues and the subcuticular tissues will be infiltrated with the remaining 50ml of peri-articular injection.[13] Following wound closure the tourniquet will be released and the "tourniquet-down time" noted on the trial documentation.

A routine pre-, peri- and post-operative analgesic medicines regimen will be used for all of the participants following hospital guidelines for TKR surgery:

Pre-medication (before surgery)

1. Gabapentin 300mg (100mg if older than 70 years or CKD stage 3)

Peri-operatively

1. Spinal: 2 mls of 0.5% heavy bupivacaine or 2 mls of 0.5% isobaric levobupivacaine (chirocaine)
2. Sedate with target controlled infusions of Propofol or General Anaesthetic if needed
3. If unable to do a spinal, use IV morphine 0.1 to 0.2mg/Kg intra operatively.
4. Paracetamol: 1g IV

Post-operatively

1. *Paracetamol 1gm QDS*
2. *Diclofenac 50mg or Ibuprofen 400mg TDS if no contraindications and to be commenced 8 hours post operatively*
3. *Gabapentin 300mg TDS or 100mg TDS for 5 days (lower dose for the over 70s or CKD stage 3*
4. *MST 20mg BD for 5 days or till needed 1st dose in recovery before spinal wears off*
5. Oramorph 10 or 20mg (maximum hourly) as required

On discharge

1. MST 10/20mg BD (to cover 5 postop days)
2. Gabapentin 300mg TDS (100mgs TDS for over 70s) (to cover 5 days post op)
3. Paracetomol 1gm QDS
4. Ibuprofen/ Diclofenac 400mg/50mg TDS

All post-operative analgesia taken by the participants, both regular and as required (prn), will be recorded. All of the participants will follow the standard UHCW post-operative rehabilitation protocol under the supervision of a physiotherapist. This involves immediate full weight bearing with the use of crutches, no restriction in flexion and the regular use of a cryocuff for cold therapy.

The fidelity with which both interventions are delivered will be captured by regular audits against the standards described. The results will be relayed to those delivering the intervention in order to improve and/or maintain ongoing protocol compliance.

Outcome assessments and time points

We will use techniques common in long-term cohort studies to ensure minimum loss to follow-up, such as collection of multiple contact addresses and telephone numbers, mobile telephone numbers and email addresses. Trial outcome assessment time points and are shown in Table 1.

Table 1: Trial outcome assessment time points

Time point	Baseline	Day 1 post op	Day 2 post op	Week 6 post op	Month 12 post op
VAS		x (before and after physio)	x (before and after physio)		
4 point pain scale		x	x		
Total use of required "as analgesia"		x	X		
Straight leg raise			x		
Knee ROM			x		
Timed up and Go			x		
Bed transfers			x		
Distance mobilised			x		
OKS	x			x	x
EQ-5D-5L	x			x	x
DN2 (7 item DN4)	x			x	x
Complications		x	x	x	x

Our primary outcome measure will use the well-established 100mm visual analogue score (VAS) reported by the participant prior to physiotherapy on first day post-operatively, as this is when the patient would be expected to get out of bed and mobilise the knee after their surgery. A further VAS measurement will be performed before physiotherapy on the second day. This will allow us to define the analgesic effect following mobilisation. Any failure to mobilise and the reason for failure will be recorded from the patient's physiotherapy record. Additional routine standard of care pain score data will be collected during the patient's hospital admission. The pain score is a four point ordinal scale. The pain data will be reviewed by the research associate and entered onto an anonymised participant data sheet. Early knee function will be assessed in both groups of patients using three basic methods:

1. Straight Leg Raise (SLR): With patient supine the participant is to attempt (unaided) to flex at the hip with knee locked in extension to raise their operated-side ankle off the bed. If the participant is able to raise ankle off bed this is deemed a positive SLR.
2. The participant is assessed in their ability to mobilise from bed to chair: (a) independently, (b) with assistance of one, (c) with assistance of two and (d) unable to mobilise.
3. Timed "Up & Go"(TUG) is a test of functional mobility. It uses the time that a person takes to rise from a chair, walk three meter's, turn around, walk back to the chair, and sit down. During the test, the patient is expected to wear their regular footwear and use any mobility aids that they would normally require. A time of >20seconds indicates impaired mobility.

At 48 hours post-operatively, participant drug charts and anaesthetic charts will be reviewed by the Research Associate and the total use of analgesia over the 48 hour period post operatively will be recorded. Opiate analgesia used will be converted to "morphine equivalent dose", see table 2.[21] Total morphine equivalent dose will be analysed at 24 and 48 hour time-points. The total dose of paracetamol and/or NSAIDS will also be reported.

Table 2: Opiate Analgesia Converted to Morphine Equivalent Dose

Opiate analgesia	Route	Typical dose	Total 24hr dose	Equivalent morphine 24hr dose	4-hrly oral morphine dose	Relative potency to oral morphine (24hr)
Codeine[21]	Oral	60mg qds	240mg	24mg	4mg	0.1
Dihydrocodeine[21]	Oral	60mg qds	240mg	24mg	4mg	0.1
Tramadol[21]	Oral	50mg qds	240mg	40mg	6.6mg	0.2

At six weeks and 12 months post-operatively all participants will asked to complete some questionnaires either at their routine clinical follow up appointment or via post. The questionnaires will ask participants to complete three validated outcome scores:

1. Oxford Knee Score (OKS) will assess participant's perceived function following their procedure. This is a validated self-administered osteoarthritis outcome measure and should only require 10 minutes to complete.[22]
2. EuroQol (EQ-5D-5L) is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale.[23 24]
3. Douleur Neuropathic Pain (DN2/Seven Item DN4) Scores, a validated screening tool for neuropathic pain consisting of two questions.[16 17]

All Adverse Events (AE) will be recorded up to 12 months after surgery. An adverse event is defined as any untoward medical occurrence in a subject and which does not necessarily have a causal relationship with the treatment. A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

1. Results in death

2. Is immediately life-threatening
3. Requires hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is an important medical condition

Suspected Unexpected Serious Adverse Reactions (SUSARS) are SAEs that are unexpected i.e. their nature or severity is not consistent with the Summary of Product Characteristics, and are considered to be caused by one or more the trial medicinal interventions.

The following (serious) adverse events will be expected and therefore will not need immediate reporting to the trial office**:** Chest Infection, Urinary Tract Infection, Myocardial Infarction, Stroke, Superficial Surgical Site Infection, Deep Surgical Site infection, Bleeding, removal/revision of metalwork, DVT/PE, Damage to nerves in the surgical area

The definitions of the EU Directive 2001/20/EC article 2 based on ICH GCP apply in this trial protocol; both investigators and sponsors will follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. SAEs that are not listed as expected are considered to be related or potentially related to the administration of the IMP. Expectedness will be determined by the Investigators using the information within the products SPC. SAEs that are deemed to be unexpected and related to the trial will be notified to the main research ethics committee, MHRA and trial sponsor within 15 days for a non-fatal or non-life threatening event and within seven days for a fatal or life threatening event. All participants experiencing serious adverse events will be followed-up as per protocol at the end of the trial and causality of SAEs assessed.

Data Management

The Case Report Forms will be designed by the trial coordinator in conjunction with the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of the Clinical Sciences Building at University Hospitals Coventry and Warwickshire. Participants will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained for at least five years after completion of the trial.

Statistical Analysis Plan

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

The main analysis will investigate differences in the primary outcome measure, the VAS pain score pre-physiotherapy on the first day post-operatively, between the two treatment groups (single injection femoral nerve block and multimodal peri-articular injection) on an intention-to-treat basis. Initial analysis will investigate differences in pain score measurements on an intention to treat basis using a t-test based on an assumed normal distribution for the primary outcome (VAS pain score). Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals. The simple t-test will be augmented with a linear regression analysis that adjusts for expected confounders of age and gender. Adjusted and unadjusted analyses will be presented together with diagnostics that assess the modelling assumptions (e.g. quantile-quantile plots). Subsidiary analyses will also test for differences at intermediate times and more generally

across all times using a repeated-measures approach (e.g. generalized estimating equations). For secondary outcome measures that can be assumed to be approximately normally distributed (e.g. OKS, EQ-5D), data will be analysed in a similar manner to VAS pain scores. However, routinely collected pain scores, measured on a four point ordinal score scale, will be analysed using the proportional-odds model and the time course modelled using appropriate methods (e.g. repolr). Counts of complications will be compared between groups using chi-squared tests.

Inevitably some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the missing data will be carefully considered including in particular whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities (e.g. mice in R). Any resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

The main analyses will be conducted using the software package R (http://www.r-project.org/), with some additional analyses in SPSS if this proves necessary. The primary focus of the statistical analysis will be the comparison of the two treatment groups, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions.

Trial Organisation, Regulation and Oversight

All issues pertaining to the management of the trial will be co-ordinated by a trial management group. A Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will be independently chaired and established in accordance with the principles of GCP and the University of Warwick standard operating procedures. The trial will be registered with the International Standard Randomised Controlled Trial Number Register, the Medicine and Healthcare Products Regulatory Agency (MHRA) UK and EudraCT. Following approval from the regulatory authorities mentioned, the study will be conforming to regulations for a Clinical Trial of an Investigations Medicinal Product (CTIMP). The blinding will only be broken for clinical management purposes. In exceptional circumstances beyond this agreement will be sought from the Chief Investigator and statistician before the blinding is broken.

For this trial levobupivacaine hydrochloride 0.25% injection, morphine sulphate injection, ketorolac trometamol injection, 1:1000 adrenaline injection and sodium chloride 0.9% injection used peri-operatively are being used as Investigational Medicinal Products (IMPs). All IMPs will be taken from commercially available stock and drug accountability logs for IMPs will be maintained by the chief investigator and those individuals with designated responsibilities. Accountability logs will record the manufacturer, batch number, expiry dates and the patient's trial number, in order to maintain traceability of the stock issued within the trial. All records will be maintained in accordance with current Good Clinical Practice (GCP) and in line with the Medicines for Human Use (Clinical Trials) Regulations 2004.

It is anticipated that the trial will be finished and the study report completed by May 2016 and the results disseminated via patient information material prepared in collaboration with NHS Choices. All key findings from the trial will be presented at national and international conferences such as

the British Orthopaedic Association (BOA) and British Association of Specialist Knee Surgeons (BASK) and we aim to publish the results in at least one major peer-reviewed publication.

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Competing Interests
None of the authors declare any competing interests

Data Sharing
No additional data will be available.

Acknowledgement
Andrew Sprowson died tragically on 13 March 2015. He was the Chief Investigator and main grant holder for this trial. Andrew was an academic orthopaedic surgeon who was dedicated to improving evidence based care in his field. He was an exceptionally enthusiastic researcher and surgeon and will be sadly missed by both his academic and clinical colleagues.

We would like to acknowledge the following additional PAKA collaborators: Thompson P, Lawrence C, Pursall R, Brown J, Clarkson L, Dube A, Stevens S and Clark T.

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Author contributions
APS developed the trial protocol and contributed to the writing of the manuscript. APS was the original Chief Investigator and grant holder for this study.
PDHW contributed to the writing of the manuscript. PDHW is the current Chief Investigator for this study.
NP developed the trial protocol and contributed to the writing of the manuscript.
JA developed the trial protocol and contributed to the writing of the manuscript.
SB developed the trial protocol and contributed to the writing of the manuscript.
MLC developed the trial protocol and contributed to the writing of the manuscript. MLC was Chief Investigator for the pilot study.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1,10
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	10
	5b	Name and contact information for the trial sponsor	10
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3
	6b	Explanation for choice of comparators	2,3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3,4,5,6,7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7,8,9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4,5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4,5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8,9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8,9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9,10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8,10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10,11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10,11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

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

BMJ Open

Protocol for a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus single agent femoral nerve blockade as analgesia for total knee arthroplasty: Perioperative Analgesia for Knee Arthroplasty (PAKA).

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Title

Protocol for a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus single agent femoral nerve blockade as analgesia for total knee arthroplasty: Perioperative Analgesia for Knee Arthroplasty (PAKA).

Registration

The study has been registered with the current controlled trials database under reference number ISRCTN 60611146 and has the following EUDRACT Number 2013-002439-10 (protocol code number PAKA-33601-AS117013)

Roles and Responsibilities

Wall PDH*[1,2] on behalf of Sprowson AP[1,2], Parsons N[1,3], Parsons H[1], Achten J[1,3], Balasubramanian S[2], Costa ML[1,3] for the Perioperative Analgesia for Knee Arthroplasty (PAKA) collaborators

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Key words: analgesia, anaesthesia, knee replacement, knee arthroplasty, orthopaedics

Abstract

Introduction:

Total knee arthroplasty (TKA) surgery causes postoperative pain. The use of peri-operative injections around the knee containing local anaesthetic, opiates and non-steroidal anti-inflammatory drugs has increased in popularity to manage pain. Theoretical advantages include reduced requirements for analgesia and earlier mobilisation. We propose a single centre randomised controlled trial of multimodal peri-articular anaesthetic infiltration versus femoral nerve anaesthetic blockade as analgesia for TKA. The aim is to determine, in patients undergoing TKA, if there is a difference in patient reported pain scores on the Visual Analogue Score (VAS) prior to physiotherapy on day one post-operatively between treatment groups.

Methods and analysis:

Patients undergoing a primary unilateral TKA at University Hospitals Coventry and Warwickshire Hospitals will be assessed for eligibility. A total of 264 patients will provide 90% power to detect a difference of 12mm on the VAS on day one post-operatively at the 5% level. The trial will use 1:1 randomisation, stratified by mode of anaesthetic. Primary outcome measure will be the VAS for pain prior to physiotherapy on day one. Secondary outcome measures include VAS on day two, total use of opiate analgesia up to 48 hours, ordinal pain scores up to 40minutes after surgery, independent functional knee physiotherapist assessment on day one and two. Oxford knee Scores (OKS), EuroQol (EQ-5D) and Douleur Neuropathic Pain Scores (DN2) will be recorded at baseline, 6

weeks and 12 months. Adverse Events (AE) will be recorded up to 12months. Analysis will investigate differences in VAS on day one between the two treatment groups on an intention-to-treat basis. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05.

Ethics and dissemination:
NRES Committee West Midlands, 23rd September 2013 (ref: 13/WM/0316). The results will be disseminated via peer-reviewed publications and conference presentations.

Strength and limitations

Strengths:

- Pragmatic design to facilitate implementation within routine clinical practice
- Optimised protocol to reduce risk of bias.
- Appropriate sample size calculation.
- Planned intention-to-treat analysis.

Limitations:

- Lack of blinding amongst clinicians delivering the intervention.
- Single centre design.

Introduction

Total knee arthroplasty (TKA) is the commonest joint replacement, with over 82,000 procedures performed annually in the National Health Service (NHS).[1] Demand is growing and this, combined with an ageing population, the frequency of TKA and its burden on the NHS increases year on year. During the last decade there has been increased interest in optimal peri-operative care to enhance recovery following TKA. Improvement of analgesia; reduction of surgical stress responses and organ dysfunctions; including nausea, vomiting and ileus; early mobilisation; and oral nutrition have all been examined. Measures to try and improve pain management have been developed including multimodal regimes which theoretically allow functional rehabilitation to be initiated more rapidly postoperatively. TKA generates substantial amounts of postoperative pain, which effects range of movement and ability to mobilise. Good pain relief with minimal physiological disturbance is important for postoperative knee rehabilitation.[2-4] Epidural analgesia is very effective in pain control but is associated with side effects such as pruritus, urinary retention and motor block.[2] Epidural analgesia can also occasionally lead to serious complications such as spinal cord ischemia, vertebral canal haematoma, vertebral canal abscess, infective meningitis, nerve and spinal cord injury, wrong route administration and cardiovascular collapse.[5]

The use of opioid drugs, administered by means of either patient-controlled analgesia or other methods, is another effective method of postoperative pain relief but is often associated with systemic side effects, including nausea and vomiting, respiratory depression, drowsiness, pruritus, reduced gut mobility, and urinary retention.[6] Drowsiness in particular may delay the patient's post-operative mobilisation. Femoral nerve block, as a single peri-operative infiltration or via an indwelling catheter, has been shown to improve post-operative pain control and reduce the use of systemic analgesics and is currently the standard care for peri-operative analgesia.[7] The key advantage of the technique is that it avoids the systemic effects associated with both epidural and opioid analgesics. However, it may be associated with complications such as vascular puncture, nerve damage, infection and diminished muscle control.[8] The inhibition of the quadriceps muscle group can delay post-operative mobilisation.[9] Since the posterior capsule of the knee joint is innervated by the branches of the sciatic nerve rather than the femoral, femoral nerve blockade may also result in incomplete pain relief. Femoral nerve block is currently the standard perioperative analgesia for TKR surgery amongst anaesthetists working within the NHS.

Recently the use of intra-operative, peri-articular infiltration of multimodal analgesics has gained in popularity. Peri-articular infiltration has the advantage of delivering drugs directly to the sources of pain, thereby avoiding systemic side effects.[10]. The concept of multimodal analgesia refers to the simultaneous administration of multiple anaesthetic agents, such as local anaesthetics, opiates and non-steroids anti-inflammatory drugs. To produce optimal pain relief combined with the lowest incidence of side effects, a multimodal pain therapy is essential.[5] This technique of analgesia was developed specifically to avoid sedation and facilitate rapid physiological recovery after lower limb arthroplasty in order to enable early mobilisation and discharge.[9-13] In contrast to femoral nerve blockade, peri-articular infiltration does not inhibit quadriceps function and also reaches the posterior capsule of the knee joint. Published studies suggest that peri-articular infiltration may reduce requirements for post-operative analgesia, lead to earlier mobilisation and discharge from hospital. However, the number of published randomised controlled trials involving TKA is small and all are underpowered and lack statistical rigour. An initial pilot study comparing femoral nerve block and multimodal peri-articular infiltration has already been completed in order to help plan and design a full trial with the following null hypothesis[14]:

Post-operative pain following primary TKA does not differ between multimodal peri-articular knee infiltration with Levobupivicaine 150mg, Morphine 10mg and Ketorolac 30mg diluted in 0.9% saline to make a volume 100ml (0.5ml 1:1000 adrenaline) and the single agent femoral nerve blockade.

These two comparators have been chosen for comparison because femoral nerve block is the current standard care for peri-operative analgesia for TKR surgery and multimodal peri-articular infiltration represents a new but now established alternative.

Objectives

The primary objective of this full trial is to quantify and draw inferences on the efficacy between treatment groups based on observed differences as shown by a validated, patient reported 100mm visual analogue pain score, pre-physiotherapy on the first post-operative day, collected by an independent physiotherapist. This is the most important outcome as pain at the time when the patient is first starting to walk and use their new knee replacement will determine the ability of the patient to mobilise. Early mobilisation is associated with improved functional outcomes and a reduced risk of complications.[15]

The secondary objectives of the study are to quantify and draw inferences on the efficacy of the treatment groups based on observed differences as shown by:

1. Visual analogue scale after physiotherapy on the first post-operative day and before and after physiotherapy on the second post-operative day.
2. The total use of opiate analgesia up to 24 and 48 hours after the operation.
3. Ordinal pain score (routinely collected up to 40 minutes after surgery).
4. Independent routine functional physiotherapist assessment on day one and two postoperatively assessing: straight leg raise, knee range of movement, Timed Up and Go, bed transfers and distance mobilised.
5. Oxford Knee Score (OKS) collected pre-operatively and 6 weeks post-operatively.
6. EuroQol (EQ-5D–5L) Score collected pre-operatively and 6 weeks post-operatively.
7. DN2 Douleur Neuropathic Pain (DN2/Seven Item DN4) Score, collected pre-operatively and 6 weeks and 12 months post-operatively.[16 17]
8. The number and type of Adverse Events (AE) up to 12 month post-operatively.

Methods and analysis

The protocol (version 5.0 dated 7th October 2015) was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[18] Approval was

obtained on the 23rd September 2013 under reference number 13/WM/0316. This study is jointly sponsored by the University of Warwick and University Hospitals Coventry & Warwickshire NHS Trust. The trial will be carried out in accordance with the Medicines for Human use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP); all collaborators will be trained in GCP, and in accordance with this protocol. This trial will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.

A single centre two arm parallel group superiority type trial design will be completed. All patients undergoing an elective primary unilateral TKA under the care of an orthopaedic consultant at University Hospitals Coventry & Warwickshire NHS Trust are potentially eligible for entry to the trial. However, patients with any of the following will not be eligible:

1. Concomitant medical or psychiatric problems which, in the opinion of the Investigator, would prevent completion of treatment or follow-up.
2. Pre-operative history of neurological abnormality in the ipsilateral leg e.g. history of stoke, neurogenic pain or previous nerve pain.
3. Specific contraindication to the analgesic agents used:
   Morphine
   i. Hypersensitivity reaction
   Ketorolac
   i. Active or previous peptic ulcer
   ii. History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy
   iii. Haemorrhagic diatheses, including coagulation disorders
   iv. Hypersensitivity to ketorolac, trometamol or other NSAIDs
   v. Moderate or severe renal impairment (serum creatinine > 160 micromol/l)
   Levobupivacaine
   i. Known hypersensitivity to levobupivacaine, local anaesthetics of the amide type or any of the excipients
   ii. Uncontrolled angina
   iii. 2nd or 3rd degree heart block
4. Participation in a clinical trial of an investigational medicinal product in the last 90 days.
5. Previous entry in the present trial.
6. Evidence that the patient would be unable to adhere to trial procedures.

Patients fulfilling the eligibility criteria will be identified by consultants and research associates in outpatient clinics. In order to ensure all eligible patients are approached for recruitment patients already on the waiting list (as identified via hospital operative planning software, Opera) for a unilateral TKA will be screened and may be contacted during their pre-operative assessment at the hospital, which normally occurs a few weeks before surgery. All appropriate patients will be approached as per ICH-GCP guidelines. Patients will be recruited by trained research associates who will help to present the trial and interventions in a consistent and unbiased manner. Recruitment by trained research associates will also be a mechanism to help ensure optimum participant enrolment.[19] Patients will only be given "Letters of Invitation" if, in the opinion of the research associate, there has been an adequate verbal introduction to the trial. Patients will be given adequate time to consider their participation in order to ensure informed consent to participate in the trial. Signed and dated informed consent will be obtained by medically trained personnel as per trust protocol for Clinical Trial Investigation of a Medicinal Product (CTIMP) study. In the event that any further information becomes available which may influence the patient's willingness to continue in the trial, the trial team will contact the participant. The participant's General

Practitioner (GP) will be informed by letter that the patient is taking/has taken part in this clinical trial. A participant may deny the research team permission to inform the GP of their trial involvement by not initialling the appropriate box on the consent form. Pre-randomisation eligibility checks will be carried out to ensure that a patient fit the eligibility criteria and is not randomised in error. Inclusion of a patient in the trial will be flagged on their clinical notes by means of a trial sticker.

Randomisation

Allocation of trial treatments will be provided through a distal randomisation service. Randomisation will be a 1:1 allocation using a computer generated randomisation schedule stratified by anaesthetic type - general or spinal block using permuted blocks of random sizes. The block sizes will not be disclosed, to ensure concealment. To ensure allocation concealment the mechanism of contact being used is via a telephone and has a stringent procedure to ensure enrolment before randomisation. Randomisation via telephone will be undertaken by a trained member of the theatre team present on the day of surgery. They will then inform the rest of the theatre team (excluding the participant) of the treatment allocation.

Sample Size

The primary outcome measure for this study is pain on day one post-operatively, assessed using a 100mm visual analogue scale (VAS). Pilot data (n=46) was used in a power analysis to estimate the sample size required for a two-arm parallel group RCT. Based on the available literature, a change in the VAS of 12 mm (95% CI 9mm-15mm) is clinically meaningful, thus these calculations assume the minimum clinical important difference (MCID) to be approximately 12mm.[20] The observed standard deviation from the pilot study was 30mm, giving a standardised effect size (MCID/SD) of 0.4, a moderate value, and of the appropriate order of magnitude for a pragmatic study of this type. Hence to power a trial to test the null hypothesis of equality of the treatments, assuming approximate normality for the VAS, would require 132 patients in each treatment arm or 264 in total - assuming 90% power, 5% significance, a standard deviation of 3cm and an MCID of 12mm. Given that the majority of data collection will occur during participant hospital stay, with the exception of the patient reported outcome measures, we anticipate loss of follow-up data will be minimal (<5%). The sample size for this trial corresponds to effects observed in previous similar studies.[20 21] These studies demonstrated effects on a 100mm visual analogue scale (VAS: our primary outcome measure) and on participant consumption of “as required” analgesia with 20-25 patients per experimental group.

Recent audit within the department indicated there are approximately 50 elective primary unilateral total knee replacements carried out per month, of whom over half would be eligible for this trial. Although not all patients will want to take part, our previous experience in trials of perioperative adjuncts to surgery has shown high levels of patient recruitment (80-100%) with only 7% declining the pilot study. Therefore we believe 11 patients per month to be a realistic recruitment figure. At this rate the entire study sample can be recruited within 24 months. However, if recruitment rate is not as high as anticipated, a sample size of 200 patients will still be adequate to identify any difference between groups with 80% power.

Participants may withdraw from the trial treatment and/or the whole trial at any time without prejudice. Unless a participant explicitly withdraws their consent they should be followed-up and data collected as per the protocol until the end of the trial.

Should a participant withdraw from the trial they would continue to be treated as per normal routine postoperative management, follow-up and clinical practice. The data collected up until the point of withdrawal would be used for analysis at the end of the trial. Subjects may be withdrawn

from the trial at the discretion of the Investigator and/or the Trials Steering Committee due to safety concerns.

Blinding

Patients will be blind to the intervention to which they are allocated, as femoral nerve blocks will be done after sedation and or anaesthetic. All interventions will be conducted within a sterile zone with drapes which will physically prevent patients seeing which intervention they receive. Due to the nature of the study it is not possible for the surgeon and anaesthetist delivering the interventions to be blinded to the treatment options. Outcome data will be collected by a research associate and an independent clinical physiotherapist who are blinded to the treatment allocation. Furthermore, the trial statistician will be blinded to the treatment allocations throughout.

Interventions

In this pragmatic trial, patients will undergo routine elective primary unilateral TKA using the standard technique of the anaesthetist and the operating surgeon. In addition, the patient will receive one of the following peri-operative analgesic interventions:

1. *Femoral Nerve Block*

Under aseptic conditions, the femoral artery will be palpated immediately below the inguinal ligament and nerve stimulation and or ultrasound will be used to identify the femoral nerve just lateral to the artery. Once the femoral nerve has been identified the block may be performed in the routine manner (15, 16) using 30 ml (75mg) of levobupivacaine hydrochloride 0.25%.

2. *Intraoperative Peri-articular Injection*

The peri-articular infiltration of multi-modal agents will involve the preparation of two 50ml syringes each containing 30ml (75mg) of levobupivacaine hydrochloride 0.25% injection, 0.5ml (5mg) morphine sulphate injection, 0.5ml (15mg) ketorolac trometamol injection and 0.25ml of 1:1000 adrenaline then diluted with 0.9% saline to make a mixture containing a total volume of 50ml. Adrenaline is added to the mixture to reduce blood loss after the operation. Each syringe will be prepared for immediate use and not stored. 50ml of the mixture will be injected into the posterior, medical and lateral soft-tissues just prior to implantation of the TKR components. Care will be taken to avoid excessive infiltration in the area of the common peroneal nerve. Then, whilst the cement is curing, the anterior soft-tissue including the quadriceps mechanism, the retinacular tissues and the subcuticular tissues will be infiltrated with the remaining 50ml of peri-articular injection.[13] Following wound closure the tourniquet will be released and the "tourniquet-down time" noted on the trial documentation.

The allocated intervention will be discontinued if there is evidence of an immediate serious adverse reaction such as anaphylaxis. Once randomised if a participant specifically requested that the intervention was discontinued or modified this would be honoured provided valid consent was obtained, however, as both interventions are delivered peri-operatively such a scenario is extremely unlikely.

A routine pre-, peri- and post-operative analgesic medicines regimen will be used for all of the participants following hospital guidelines for TKR surgery:

Pre-medication (before surgery)

1. Gabapentin 300mg (100mg if older than 70 years or CKD stage 3)

Peri-operatively

1. Spinal: 2 mls of 0.5% heavy bupivacaine or 2 mls of 0.5% isobaric levobupivacaine (chirocaine)

2. Sedate with target controlled infusions of Propofol or General Anaesthetic if needed
3. If unable to do a spinal, use IV morphine 0.1 to 0.2mg/Kg intra operatively.
4. Paracetamol: 1g IV

Post-operatively

1. *Paracetamol 1gm QDS*
2. *Diclofenac 50mg or Ibuprofen 400mg TDS if no contraindications and to be commenced 8 hours post operatively*
3. *Gabapentin 300mg TDS or 100mg TDS for 5 days (lower dose for the over 70s or CKD stage 3*
4. *MST 20mg BD for 5 days or till needed 1st dose in recovery before spinal wears off*
5. Oramorph 10 or 20mg (maximum hourly) as required

On discharge

1. MST 10/20mg BD (to cover 5 postop days)
2. Gabapentin 300mg TDS (100mgs TDS for over 70s) (to cover 5 days post op)
3. Paracetomol 1gm QDS
4. Ibuprofen/ Diclofenac 400mg/50mg TDS

All post-operative analgesia taken by the participants, both regular and as required (prn), will be recorded. All of the participants will follow the standard UHCW post-operative rehabilitation protocol under the supervision of a physiotherapist. This involves immediate full weight bearing with the use of crutches, no restriction in flexion and the regular use of a cryocuff for cold therapy.

The fidelity with which both interventions are delivered will be captured by regular audits against the standards described. The results will be relayed to those delivering the intervention in order to improve and/or maintain ongoing protocol compliance.

Outcome assessments and time points

We will use techniques common in long-term cohort studies to ensure minimum loss to follow-up, such as collection of multiple contact addresses and telephone numbers, mobile telephone numbers and email addresses. Trial outcome assessment time points and are shown in Table 1.

Table 1: Trial outcome variables, analysis metric, aggregation method and time points

Outcome variable	Analysis metric	Aggregation	Time Point				
			Baseline	Day 1 post op	Day 2 post op	Week 6 post op	Month 12 post op
VAS (0-100mm)	Final value	Mean		x (before and after physio)	x (before and after physio)		
4 point pain scale	Final value	Proportion and type		x	x		
Total use of opiate analgesia (mg)	Final value	Mean		x	x		

Straight leg raise (yes/no)	Final value	Proportion		x	x		
Knee ROM (degrees)	Final value	Mean		x	x		
Timed up and Go (impaired mobility yes/no)	Final value	Proportion		x	x		
Bed transfers (4 point ordinal scale)	Final value	Proportion and type		x	x		
Distance mobilised (metres)	Final value	Mean		x	x		
OKS	Final value	Mean	x			x	x
EQ-5D-5L	Final value	Mean	x			x	x
DN2 (7 item DN4 ordinal scale)	Final value	Proportion	x			x	x
Adverse Events	Final value	Proportion and type		x	x	x	x

Our primary outcome measure will use the well-established 100mm visual analogue score (VAS) reported by the participant prior to physiotherapy on first day post-operatively, as this is when the patient would be expected to get out of bed and mobilise the knee after their surgery. The mean VAS score will be reported for both treatment groups. A further VAS measurement will be performed before physiotherapy on the second day. This will allow us to define the analgesic effect following mobilisation. Any failure to mobilise and the reason for failure will be recorded from the patient's physiotherapy record. Additional routine standard of care pain score data will be collected during the patient's hospital admission. The pain score is a four point ordinal scale. The pain data will be reviewed by the research associate and entered onto an anonymised participant data sheet. Early knee function will be assessed by an independent physiotherapist in both groups of patients using four basic methods:

1. Straight Leg Raise (SLR): With patient supine the participant is to attempt (unaided) to flex at the hip with knee locked in extension to raise their operated-side ankle off the bed. If the participant is able to raise ankle at least 5cm off bed the bed they are deemed to be able to SLR. The proportion of participants able to SLR in each group will be reported.
2. Knee range of movement: The patient's own active knee range of motion to both extension and flexion will be measured in degrees. The mean knee ROM in each group will be reported.
3. The participant is assessed in their ability to transfer from bed to chair: (a) independently, (b) with assistance of one, (c) with assistance of two and (d) unable to mobilise. The proportion of participants in each group will be reported for this ordinal scale.
4. Timed "Up & Go"(TUG) is a test of functional mobility. It uses the time that a person takes to rise from a chair, walk three meter's, turn around, walk back to the chair, and sit down. During the test, the patient is expected to wear their regular footwear and use any mobility aids that they would

normally require. A time of >20seconds indicates impaired mobility. The proportion of participants with impaired mobility in each group will be reported.

At 48 hours post-operatively, participant drug charts and anaesthetic charts will be reviewed by the Research Associate. Opiate analgesia used will be converted to "morphine equivalent dose", see table 2.[22] Total morphine equivalent dose used up to 24 and 48 hour post operatively will be recorded for each participant in milligrams and the mean dose reported for each treatment group. The total dose of paracetamol and/or NSAIDS will also be reported.

Table 2: Opiate Analgesia Converted to Morphine Equivalent Dose

Opiate analgesia	Route	Typical dose	Total 24hr dose	Equivalent morphine 24hr dose	4-hrly oral morphine dose	Relative potency to oral morphine (24hr)
Codeine[22]	Oral	60mg qds	240mg	24mg	4mg	0.1
Dihydrocodeine[22]	Oral	60mg qds	240mg	24mg	4mg	0.1
Tramadol[22]	Oral	50mg qds	240mg	40mg	6.6mg	0.2

At six weeks and 12 months post-operatively all participants will asked to complete some questionnaires either at their routine clinical follow up appointment or via post. The questionnaires will ask participants to complete three validated outcome scores:

1. Oxford Knee Score (OKS) will assess participant's perceived function following their procedure. This is a validated self-administered osteoarthritis outcome measure and should only require 10 minutes to complete.[23] The mean final value for OKS will be reported for both treatment groups at six weeks and 12 months.
2. EuroQol (EQ-5D-5L) is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale.[24 25] The mean final value for EQ-5D-5L will be reported for both treatment groups at six weeks and 12 months.
3. Douleur Neuropathic Pain (DN2/Seven Item DN4) Scores, a validated screening tool for neuropathic pain consisting of two questions.[16 17] The proportion of participants with evidence of neuropathic pain in each group will be reported.

All AEs will be recorded up to 12 months after surgery. An AE is defined as any untoward medical occurrence in a subject and which does not necessarily have a causal relationship with the treatment. A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

1. Results in death
2. Is immediately life-threatening
3. Requires hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is an important medical condition

Suspected Unexpected Serious Adverse Reactions (SUSARS) are SAEs that are unexpected i.e. their nature or severity is not consistent with the Summary of Product Characteristics, and are considered to be caused by one or more the trial medicinal interventions.

The following (serious) adverse events will be expected and therefore will not need immediate reporting to the trial office**:** Chest Infection, Urinary Tract Infection, Myocardial Infarction, Stroke, Superficial Surgical Site Infection, Deep Surgical Site infection, Bleeding, removal/revision of metalwork, DVT/PE, Damage to nerves in the surgical area. The total number, type (with proportions) of adverse events will be reported for both groups

Data Management

The Case Report Forms will be designed by the trial coordinator in conjunction with the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of the Clinical Sciences Building at University Hospitals Coventry and Warwickshire. Participants will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained for at least five years after completion of the trial.

Statistical Analysis Plan

Standard statistical summaries (e.g. means and variances, medians and ranges or proportions dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

The main analysis will investigate differences in the primary outcome measure, the VAS pain score pre-physiotherapy on the first day post-operatively, between the two treatment groups (single injection femoral nerve block and multimodal peri-articular injection) on an intention-to-treat basis. Initial analysis will investigate differences in pain score measurements on an intention to treat basis using a t-test based on an assumed normal distribution for the primary outcome (VAS pain score). Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals. The simple t-test will be augmented with a linear regression analysis that adjusts for expected confounders of age and gender. Adjusted and unadjusted analyses will be presented together with diagnostics that assess the modelling assumptions (e.g. quantile-quantile plots). Subsidiary analyses will also test for differences at intermediate times and more generally across all times using a repeated-measures approach (e.g. generalized estimating equations). For secondary outcome measures that can be assumed to be approximately normally distributed (e.g. OKS, EQ-5D), data will be analysed in a similar manner to VAS pain scores. However, routinely collected pain scores, measured on a four point ordinal score scale, will be analysed using the proportional-odds model and the time course modelled using appropriate methods (e.g. repolr). Counts of adverse events will be compared between groups using chi-squared tests.

Inevitably some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the missing data will be carefully considered including in particular whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities (e.g. mice in R). Any resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

The main analyses will be conducted using the software package R (http://www.r-project.org/), with some additional analyses in SPSS if this proves necessary. The primary focus of the statistical analysis will be the comparison of the two treatment groups, and this will be reflected in the

analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions.

Trial Organisation, Regulation and Oversight

All issues pertaining to the management of the trial will be co-ordinated by a trial management group (TMG). The TMG comprises the chief investigator, trial manager, co-investigators, trial statistician and the hospital site (UHCW) principal investigator.

The Data Monitoring Committee (DMC) comprises an independent chair with relevant experience in trial statistics, the trial statistician and the trial manager. The main roles of the DMC will be to review/approve the Statistical Analysis Plan (SAP), and to review trial progress, interim data and safety aspects of the study.

The Trial Steering Committee (TSC) comprises an independent chair, chief investigator, trial manager, co-investigator, statistician, an independent public representative and sponsor representative. The remit of the TSC is to:

- Monitor and supervise the progress of the trial towards its interim and overall objectives.
- Review at regular intervals relevant information from other sources.
- Consider the recommendations of the DMC.
- Inform the funding body on the progress of the trial.

Any proposed changes to the protocol will first be reviewed by the TSC and if approved then submitted for independent review and approval by the trial sponsor and local REC. Substantive amendments defined as changes that may affect the safety of trial participants or the scientific validity, scope, or ethical rigour of the trial will also be communicated to the trial registries and funding body. All approved protocols will be marked by a version number and date.

The trial is registered with the International Standard Randomised Controlled Trial Number Register, the Medicine and Healthcare Products Regulatory Agency (MHRA) UK and EudraCT. The study will conform to regulations for a CTIMP. The blinding will only be broken for clinical management purposes. In exceptional circumstances beyond this agreement will be sought from the Chief Investigator and statistician before the blinding is broken.

For this trial levobupivacaine hydrochloride 0.25% injection, morphine sulphate injection, ketorolac trometamol injection, 1:1000 adrenaline injection and sodium chloride 0.9% injection used peri-operatively are being used as Investigational Medicinal Products (IMPs). All IMPs will be taken from commercially available stock and drug accountability logs for IMPs will be maintained by the chief investigator and those individuals with designated responsibilities. Accountability logs will record the manufacturer, batch number, expiry dates and the patient's trial number, in order to maintain traceability of the stock issued within the trial. All records will be maintained in accordance with current Good Clinical Practice (GCP) and in line with the Medicines for Human Use (Clinical Trials) Regulations 2004.

The allocated recruitment period for the trial is 24 months. Recruitment began in December 2013 and is due to finish in December 2015. Once recruited participants are randomised to a treatment allocation within three months and then followed up for 12 months. It is anticipated that the trial will be finished by March 2017. The trial has been funded for participant follow-up to 6 weeks after surgery and a study report to the funders is anticipated by May 2016.

Ethics and Dissemination

The definitions of the EU Directive 2001/20/EC article 2 based on ICH GCP apply in this trial protocol. Both investigators and sponsors will follow specific procedures when notifying and reporting adverse events/reactions in this trial. SAEs that are not listed as expected will be considered to be related or potentially related to the administration of the IMP. Expectedness will be determined by the Investigators using the information within the products SPC. SAEs that are deemed to be unexpected and related to the trial will be notified to the main research ethics committee, MHRA and trial sponsor within 15 days for a non-fatal or non-life threatening event and within seven days for a fatal or life threatening event. All participants experiencing SAEs will be followed-up as per protocol at the end of the trial and causality of SAEs assessed.

Participant in the study are covered by indemnity for negligent harm through the standard NHS Indemnity arrangements. The University of Warwick has insurance to cover for non-negligent harm associated with the protocol. The liability of the manufacturer of medicinal products being administered is strictly limited to those claims arising from faulty manufacturing of the product.

The results of the trial will be disseminated via patient information material prepared in collaboration with NHS Choices. All key findings from the trial will be presented at national and international conferences such as the British Orthopaedic Association (BOA) and British Association of Specialist Knee Surgeons (BASK) and we aim to publish the results in at least one major peer-reviewed publication.

Funding and Sponsorship

This study protocol presents independent research funded by the National Institute for Health Research (NIHR) under the Research for Patient Benefit Scheme: PB-PG-0212-27098. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health

The study is jointly sponsored by the University of Warwick (Mrs Jane Prewitt) and University Hospitals Coventry & Warwickshire NHS Trust (Mrs Ceri Jones). The trial sponsors provide ultimate approval of all new versions of the protocol before they become live. Both the funders and sponsors are required to provide final approval before publication of any study material.

Competing Interests

None of the authors declare any competing interests

Data Sharing

The final trial dataset will be available to the TSC and reported by the TMG. Once the results of the trial including the 12 month outcome data have been reported and published third party requests to access the anonymised final dataset will be considered from other research groups by the TSC. There are currently no plans to make the final dataset freely available to the general public.

Acknowledgement

Andrew Sprowson died tragically on 13 March 2015. He was the Chief Investigator and main grant holder for this trial. Andrew was an academic orthopaedic surgeon who was dedicated to improving evidence based care in his field. He was an exceptionally enthusiastic researcher and surgeon and will be sadly missed by both his academic and clinical colleagues.

We would like to acknowledge the following additional PAKA collaborators: Thompson P, Lawrence C, Pursall R, Brown J, Clarkson L, Dube A, Stevens S and Clark T.

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Author contributions

APS developed the trial protocol and contributed to the writing of the manuscript. APS was the original Chief Investigator and grant holder for this study.

PDHW contributed to the writing of the manuscript. PDHW is the current Chief Investigator for this study.

NP developed the trial protocol and contributed to the writing of the manuscript.

HP developed the trial protocol and contributed to the writing of the manuscript.

JA developed the trial protocol and contributed to the writing of the manuscript.

SB developed the trial protocol and contributed to the writing of the manuscript.

MLC developed the trial protocol and contributed to the writing of the manuscript. MLC was Chief Investigator for the pilot study.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	12,13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9,10

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7,8,9

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8,9,10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10,11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10,11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

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