A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study.

Short title: Facet-joint feasibility study

Sponsor: Barts Health NHS Trust

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Chief Investigator agreement page

The clinical study as detailed within this research protocol (version 6, dated 7th May 2016), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Statistician agreement page

The clinical study as detailed within this research protocol (version 6, dated 7th May 2016), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Principal Investigator agreement page

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Principal Investigator name: Dr Saowarat Snidvongs

Principal Investigator site: Barts Health NHS Trust

Signature and date:

Principal Investigator agreement page

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Principal Investigator name: Dr Simon Thomson

Principal Investigator site: Basildon and Thurrock University Hospitals NHS Foundation Trust

Signature and date:

Principal Investigator agreement page

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Principal Investigator name: Dr Manohar Sharma

Principal Investigator site: The Walton Centre NHS Foundation Trust

Signature and date:

Lead Collaborator: **Professor Richard Langford**

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Study summary

Title	**A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study.**
Short title	Facet-joint feasibility study
Protocol version number and date	Protocol version 6 7th May 2016
Methodology	Multicentre, double-blind, randomised controlled trial
Study duration	21 months
Study centres	Barts Health NHS Trust (also the co-ordinating centre) Basildon and Thurrock University Hospitals NHS Foundation Trust The Walton Centre NHS Foundation Trust
Objectives	This study seeks to examine the feasibility of undertaking a fully powered double-blind randomised controlled trial ('definitive trial') to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration. The definitive trial will be deemed feasible if we can demonstrate successful standardisation of the method of injection and the test-run of the sham procedure, that the proposed study design is deemed acceptable by patients and clinicians, and we are able to recruit and retain sufficient patients.
Phase of the trial	IV
Number of patients	150 patients will be recruited for the study, of which 60 patients (40% of all recruited) will be expected to have a positive response to the diagnostic test. These 60 patients will be randomised and equally allocated to intervention and control groups.
Main inclusion criteria	1. Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific low back pain. 2. Low back pain of three months or greater duration.. 3. Average pain intensity score of 4/10 or more in the seven days preceding recruitment despite NICE recommended treatment. 4. Dominantly paraspinal (not midline) tenderness at two bilateral lumbar levels.

	5. At least two components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture, and manual therapy.
Statistical methodology and analysis	As this is a feasibility study, we do not propose to formally inferentially test differences in outcomes or costs between or within the groups. Recruitment and attrition rates will be calculated with 95% confidence intervals. We shall report mean and standard deviations for primary and secondary outcomes for the two groups at baseline and all follow-up visits.

Glossary of terms and abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European Union Drug Regulating Authorities Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
JRMO	Joint Research Management Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug

Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

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1. Introduction

1.1. Background and rationale

Pain of lumbar facet-joint origin is a common cause of low back pain in adults (Savigny *et al.* 2009)[1], and may lead to chronic pain and disability, with associated health and socioeconomic implications. Lumbar facet-joints are paired synovial joints between the superior and inferior articular processes of consecutive lumbar vertebrae, and between the fifth lumbar vertebra and the sacrum. Encapsulated nerve endings have been demonstrated in these facet-joints, supplied by medial branches of the dorsal rami nerves ('medial branch nerves'). Facet-joint pain is defined as pain that arises from any structure that is part of the facet-joints, including the fibrous capsule, synovial membrane, hyaline cartilage, and bone.

At present there is no definitive research to support the use of targeted lumbar facet-joint injections to manage this pain. An extensive literature search has revealed a number of low quality studies with flawed study designs and inconsistent diagnostic and treatment methods. One systematic review found that of the six randomised trials identifying the effective of lumbar facet-joint injections, five did not use controlled diagnostic blocks and were excluded (Datta *et al.* 2009)[2]. The same review paper also looked at observational studies evaluating the role of lumbar facet-joint injections, but none of the fifteen papers identified met the inclusion criteria for the study; outcomes were followed-up for less than six months, inappropriate or inadequate statistical tests were performed, or no controlled diagnostic blocks were used.

There remains a lack of clear consensus in diagnostic criteria for lumbar facet-joint pain, as clinical and radiological findings do not correlate well with symptom severity. The technique of facet-joint injection is not standardised; some practitioners may, for example, carry out non-targeted injections in the back without radiological guidance to confirm needle placement. There is no consensus on what would constitute a suitable sham procedure for facet-joint injections (Schütz *et al.* 2011)[3]. Further confusion and uncertainty arise from the different approaches to the treatment of suspected facet-joint disease. Many practitioners employ injections of local anaesthetic and/or steroid, whilst others regard these injections as of only diagnostic or short-term value, preferring instead denervation of the facet-joint by an ablative treatment modality with the aim of achieving longer-term improvement (Nath *et al.* 2008)[4].

Due to the lack of high quality, robust clinical evidence the National Institute for Clinical Excellence (NICE) guidelines published in 2009 did not recommend injections of therapeutic substances into the back for non-specific low back pain (Savigny *et al.* 2009)[1], despite their potential to reduce pain intensity and rehabilitation. As a result, NICE called for further research to be undertaken to clarify the clinical effectiveness and cost-effectiveness of interventional pain procedures for the treatment of low back pain.

There exists no gold standard for the diagnosis of lumbar facet-joint pain, which often remains a clinical one, based on history and examination to elicit tenderness over the facet-joints, referred leg pain above the knees, and worsening pain on extension, flexion and rotation. Clinical trials in particular support the finding of lumbar paravertebral tenderness as being indicative of facetogenic pain (Cohen *et al.* 2007)[5]. Nevertheless whilst there remains little formal data on the diagnostic accuracy of medial branch nerve blocks in the management of lumbar facet-joint pain, recent evidenced-based reviews concluded that a positive response to diagnostic block (defined as a 50% or greater pain reduction) should be included in the case selection of candidates for its treatment (van Kleef *et al.* 2010, Manchikanti *et al.* 2009, Boswell *et al.* 2007)[6, 7, 8].

As there is no widely accepted consensus on the technique of facet-joint injections (FJIs) and sham procedure, the Principal Investigators have consulted 250 interventional pain specialists in the UK in order to standardise the technique for both FJIs and sham. The choice of needle, injectate and volume of injection has been determined by expert consensus. A novel approach has been designed for the sham procedure, due to the lack of published, standardised, validated sham procedures. To date, only one clinical trial of FJIs has been identified that describes in detail a sham and placebo FJI (Schütz *et al.* 2011)[3]. The 'placebo FJI' involved injection of normal saline to the peri-articular space, and outcomes were measured at 30 to 60 minutes only.

Before undertaking a full trial to assess clinical effectiveness and cost effectiveness of FJIs compared to sham (placebo) procedure for non-specific low back pain, there are a number of questions that first need to be assessed by a feasibility study:

1. Given the multiple sites with potential to generate back pain, can patient selection criteria be optimised, using clinical and investigative diagnostic methods?

2. Can the method of injection be standardised, and an appropriate sham procedure be established?

3. Can justification for further studies to evaluate treatment methods to target and attenuate the source of chronic LBP of facet-joint origin be delivered?

4. Is a sham-controlled trial design acceptable to patients and clinicians?

5. Can sufficient patients be recruited and retained?

1.2. Health technologies being assessed

Facet-joint injections of local anaesthetic and steroid for non-specific low back pain

Facet-joint injections (FJIs), the sham procedures and diagnostic tests will be performed in day surgery units at each of the three main centres. They will be carried out only by appropriately qualified members of the research team (Fellows of the Faculty of Pain Medicine of the Royal College of Anaesthetists), adhering to strict aseptic conditions and following local site theatre protocols with regards to admission and discharge criteria. The following sections (1.2.1 to 1.2.3) are procedure guidelines only; this study will be carried out at three different sites and local guidelines for interventional pain procedures will vary between sites.

1.2.1. Facet-joint injections

Method

A spinal needle will be placed within the facet-joint under X-ray guidance, and 0.5ml 0.5% bupivacaine with 20mg methylprednisolone injected per joint. Four facet-joints will be injected, at two bilateral lumbar levels.

Notes

No more than four facet-joints will be injected to avoid any potential confounding effect attributable to the systemic action of exceeding 80mg methylprednisolone. The volume of injectate will not exceed 1ml per joint, as it is possible to rupture the intra-articular capsule with volumes of greater than 1ml, spreading the local anesthetic and steroid to other potential pain-generating structures.

Identification of facet-joints

The facet-joints are paired synovial joints between the superior and inferior processes of the vertebrae at each level of the spine. They are load-bearing joints and are easily identifiable on radiographic imaging such as X-rays. The patient will attend the day surgery unit at their respective trial centre. The procedure is carried out in the prone position, with the back exposed. The investigator will examine the patient's back to elicit para-spinal tenderness of the lumbar facet-joints – these are the joints to be injected and the spinal level will be identified using image intensification (the C-arm can be rotated obliquely to facilitate this). A spinal needle (e.g. 22G 90mm Quinke) will be advanced through skin, subcutaneous tissues and paraspinal muscle, towards the facet-joint under X-ray guidance. Entry of the needle into the facet-joint

will be confirmed by visualisation of the needle position within the joint space, and local anesthetic and steroid will be injected into the facet-joint.

1.2.2. Sham procedure

Method

A spinal needle will be placed in the peri-articular space surrounding the facet-joint under X-ray guidance, at each of the four painful areas at two bilateral lumbar levels. Normal saline (0.9% sodium chloride) 0.5ml will be injected through each needle.

Para-spinal tenderness will be elicited as before (section 1.2.1), and the needle inserted under X-ray guidance to confirm placement in the peri-articular space. A small volume of normal saline will be injected away from the joint capsule, to avoid irritation of any structure that is part of the facet-joints, including the fibrous capsule, synovial membrane, hyaline cartilage, and bone. The sham group will not receive systemic steroid administration, as it has been shown that the addition of parenteral steroid makes no contribution to the pain relief achieved by targeted injections (Bogduk 2005)[9].

1.2.3. Combined physical and psychological programme

Trained physiotherapists will deliver the combined physical and psychological programme (CPP). Recent research on combined (psychological and physiotherapy) management of low back pain has demonstrated that equally effective management can be achieved with much less than the 100 hours prescribed in the 2009 NICE guidance (Savigny *et al.* 2009)[1]. The study therefore proposes to deliver a programme drawing on evidence from the BeST trial (Lamb *et al.* 2010)[12].

Physiotherapists are listed on the site delegation log and will be trained to deliver the Back Skills Training Programme by the lead physiotherapist. Individual physiotherapists will initially undertake on-line training at www.backskillstraining.co.uk to receive a certificate of completion, which is expected to take approximately 10 hours to complete. The trial lead physiotherapist will be on the study coordinating log and will organise a face-to-face meeting with each physiotherapist to ensure competency and standardised delivery. Each physiotherapist will be given a trainer manual to support CPP delivery.

Patients will undergo between four and six sessions of CPP, lasting 1.5 hours each. Completion of the CPP is defined as having completed a minimum of four but up to six sessions[10, 11, 12]. The session contents will address the following:

1. Understanding pain.

2. Pain fluctuations

3. Unhelpful thoughts and feelings

4. Restarting activities or hobbies

5. When pain worries us.

6. Coping with flare-ups

One session per programme will be observed by the trial lead physiotherapist to assess consistency of delivery and to provide feedback and support for the physiotherapists running the course. We will assess the consistency of CPP delivery across the three centres by on-site visits by the trial lead physiotherapist. A flexible supervision will provide discussion face-to-face on site visits or via phone or email.

Each participant will receive a Back Skills Training Workbook which records the dates and times of sessions attended, in addition to a stretching log, strengthening log, record of goals and fitness goals, baseline activity, unhelpful thoughts, plans to restart a feared movement or activity, relaxation log, distraction techniques, and coping strategies for pain flare-up. The original copies of the patient workbook will be kept securely as source data with the case report forms. The data from the workbooks will not be collected as part of the study, but will be used by the site physiotherapists as part of routine clinical care only.

Patients will be in groups of fewer than ten participants: we anticipate 4 to 5 groups of 4 to 5 patients per site. Therefore, supervision will be provided during the course of the trial by the research fellow on average of 1.5 hours per group run. It will usually be centred to focus on difficulties encountered in the groups, for example, difficulties in setting goals with some individuals.

Content of CPP sessions:

Assessment • History taking including current problems and eliciting beliefs on LBP and activity • Collaborative goal setting with plan to start activity goal • Exercises chosen collaboratively from options with level negotiated • Exercises practised and progression discussed
Session 1; Understanding pain • Group activity to demonstrate hurt ≠ harm • Current thinking on causes of long-term pain explained • Discussion on groups experience of alternative treatments for LBP with reference to research evidence and need to self-manage **Benefits of exercise** • Discussion of physical impact of inactivity or altered activity and how changes impact on pain (disuse syndrome) • Discussion on effects of activity / exercise • Introduction to LBP model
Session 2; Pain fluctuations • Over / underactivity cycle explained • Use of pacing • Group problem solving for a specific task that tends to be 'overdone' e.g. gardening **Working out starting point for exercises or activities** • How to use baseline setting **How to set goals** • SMART system used to break down an example goal • Feedback from group on how progressing with goals from assessment • Group problem solving problems with goals
Session 3; Unhelpful thoughts and feelings • Styles of unhelpful thinking discussed including catastrophising • Link with unhelpful behaviours • Identifying unhelpful thoughts • Group problem solving for challenging unhelpful thoughts **Relaxation (cont'd in session 4)** • Discussion on ways of relaxing and benefits • Four styles practised in session; relaxed breathing, tense/relax, autogenic and imagery
Session 4; Restarting activities or hobbies • Discussion on activities commonly avoided in LBP • Fear avoidance cycle • Group problem solving out of cycle • Development of specific goals relating to restarting activities
Session 5; When pain worries us • Effect of attention to pain explored through group activity • Hypervigilance cycle used to link unhelpful thoughts and behaviours • Group problem solving out of cycle • Discussion on the use of medication / distraction / alternating activities
Session 6; Coping with flare-ups • Discussion on causes of flare-ups • Plan of what to do in and out of flare-ups • Revision of topics over previous sessions and questions

1.3. Preclinical data

This section is not applicable to the study.

1.4. Clinical data

A systematic review was carried out, using methods described in the Cochrane Handbook for Systematic Review of Interventions (Higgins and Green 2011)[13]. A MEDLINE database search was carried out (1966 to

October 2012) and a reference list of identified articles for any additional papers checked. Please refer to section 1.1 for details of the literature search.

2. Trial objectives and design

2.1. Trial aims

The aim of this study is to assess the feasibility of conducting a definitive trial to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

The definitive trial will be deemed feasible if it can demonstrate successful standardisation of the method of injection and the test-run of the sham procedure, that the proposed study design is deemed acceptable by patients and clinicians, and that the investigators are able to recruit and retain sufficient patients.

2.2. Trial objectives

Specific objectives of this feasibility study are:

1. To assess the eligibility criteria, recruitment and retention of patients in the two treatment arms (FJI versus sham procedure) by

    a. Assessing the feasibility of recruitment in the three centres, with regards to a potential definitive trial.

    b. Reviewing the number of completed patient data sets.

    c. Auditing the quality of data entry at the centres.

    d. Assessing and analysing any protocol violations (such as failure to deliver the combined physical and psychological programme), side effects and other adverse outcomes.

2. To assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams.

3. To assess the feasibility of the proposed definitive trial design including:

a. Testing of randomisation and blinding procedures.

b. Development of an appropriate active and sham procedure for FJIs.

c. Assessment of the consistency of the trial sites to deliver the combined physical and psychological programme.

d. Ability to collect the outcomes proposed for the main trial (pain, functioning, health-related quality of life, anxiety and depression, health care resource utilisation, complications, and adverse events).

4. To estimate outcome standard deviation to inform the power calculation for a definitive trial.

5. To finalise the protocol design, statistical plan, number of centres required and study duration of the definitive trial.

2.3. Trial design

This feasibility study is a double blind two-arm randomised controlled study. Patients with non-specific low back pain of three months' duration or greater, with clinical indicators for pain of facet-joint origin and who have a positive response to a diagnostic block will be individually randomised in a 1:1 ratio to receive either the facet-joint injection (intervention group) or a sham (placebo injection) procedure (control group). Both intervention and control patients will receive a combined physical and psychological programme (CPP) after their injections.

2.3.1. Randomisation

Patients will be allocated to intervention and control and minimisation used to ensure between group balance by centre and baseline pain scores. The allocation sequence will be computer-generated and to ensure concealment, will be provided through a password protected web-based portal. The randomization procedure will be developed and maintained by the Peninsula Clinical Trials Unit (PenCTU), a United Kingdom Clinical Research Collaboration (UKCRC) accredited unit.

2.3.2. Blinding protocol

The preparation and administration of injections will be carried out by the operator (the site's Principal Investigator). The operator needs to be aware of the randomisation, as the sham injection is peri-articular, whereas the active injection is intra-articular. The PI of each site is unblinded.

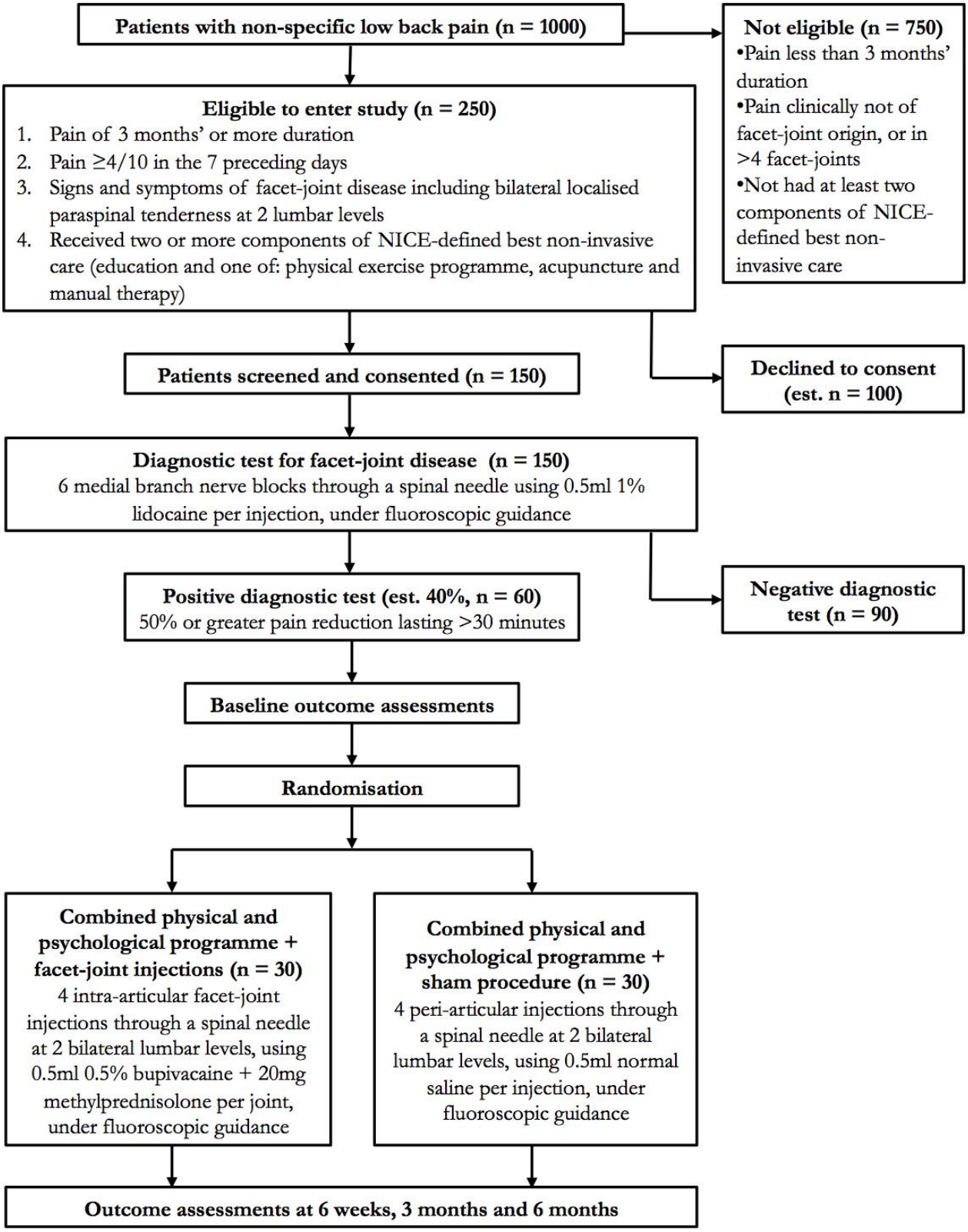
Thereafter, patient visits will be conducted by each site's research nurse (blinded), who will not have been present at the time of the FJI procedure, remains blinded, and will be responsible for collection of the study outcome data.

There will be in addition blinded medically qualified members of the research team, including the sub-investigators, to perform event assessments and other medical responsibilities.

2.4. Trial duration

Patients will be expected to take part in the study for approximately 6 months from the time of their injections (facet-joint injection or sham procedure). The study will end once they have completed their final set of questionnaires.

2.5. Study scheme diagram



3. Subject selection

3.1. Number of subjects and subject selection

Patients will be recruited from pain, spinal and musculoskeletal clinics at the three participating NHS centres and their associated community based pain clinics. Patients will be referred by their general practitioners as a standard clinical referral with low back pain requiring further specialist assessment, for reasons such as uncertain diagnosis, failure of conservative treatment, or expectation of therapeutic interventions. Approximately 1000 patients with non-specific low back pain will be identified in a multidisciplinary pain clinic, after a consensus from pain clinician and physiotherapist, over the 6-month recruiting period. We will document the relevant information in the medical notes (either in the clinic letter or a separate CRS entry)

3.2. Inclusion criteria

1. Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific low back pain[a].

2. Low back pain of three months' or greater duration.

3. Average pain intensity score of 4/10 or more in the seven days preceding recruitment despite NICE recommended treatment[b].

4. Dominantly paraspinal (not midline) tenderness at two bilateral lumbar levels.

5. At least two components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture, and manual therapy (Savigny *et al.* 2009)[1].

6. Patients are suitable for the facet-joint injections.

3.3. Exclusion criteria

1. Patient refusal to consent

[a] Clinical indicators for pain of facet-joint origin include tenderness over the facet-joints, referred leg pain above the knees, and worsening pain on extension, flexion and rotation.

[b] NICE recommends providing patients with advice and information to promote self-management of their low back pain, and offering one of the following treatments, taking into account patient preference: an exercise programme, a course of manual therapy, or a course of acupuncture (Savigny *et al.* 2009)[1].

2. More than four painful lumbar facet-joints[c].

3. Patient has not completed at least two components of NICE-recommended best non-invasive care, including education and one of a physical exercise programme, acupuncture, and manual therapy (Savigny *et al.* 2009)[1].

4. 'Red flag' signs. These are possible indicators of serious spinal pathology, and include thoracic pain, fever, unexplained weight loss, bladder or bowel dysfunction, progressive neurological deficit, and saddle anaesthesia (Greenhalgh and Selfe 2010[14]).

5. Known hypersensitivity to study medications.

6. Dominantly midline tenderness over the lumbar spine, any other dominant pain or radicular pain.

7. Any major systemic disease or mental health illness that may affect the patient's pain, disability and/or their ability to exercise and rehabilitate, as judged by the Principal Investigators.

8. Any active neoplastic disease, including primary or secondary neoplasm.

9. Pregnant or breastfeeding patients (Verbal confirmation will be obtained at screening. Prior to each interventional procedure involving X-rays, local hospital procedures will be followed to confirm that female participants are not pregnant).

10. Any evidence of previous lumbar facet-joint injections, previous lumbar spinal surgery or any major trauma or infection to the lumbar spine.

11. Patients with morbid obesity (body mass index of 35 or greater).

12. Participation in another clinical trial of a investigational medicinal product or disease related intervention in the past thirty days.

13. Patients unable to commit to the six-month study duration.

14. Patients involved in legal actions or employment or benefit tribunals related to their low back pain.

15. Patients with a known history of substance abuse.

[c] Up to six facet-joint injections have been chosen in order to limit the total dose of intra-articular steroids.

3.4. Criteria for premature withdrawal

Patients are free to withdraw from the study at any time and without giving a reason. The Participant Information Sheet states that 'a decision to withdraw from the study at any time will not affect the standard of care that [the patient receives] now or in the future'. Should participants choose to withdraw, they will receive an appointment to be followed up in the pain clinic, for continuing assessment and management by their pain physician.

This is a feasibility study and one of the outcomes includes evaluating what the progression/stopping rules of further trials will be.

The trial may be electively stopped at the discretion of the CI, Trial committees or Sponsor. Criteria include the reports of toxicity or adverse patient outcome.

3.5. Diagnostic test

Method

Diagnostic medial branch nerve blocks will be carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

The rationale for carrying out diagnostic medial branch nerve blocks is because of their safety, simplicity and prognostic value (van Kleef *et al.* 2010)[6]. A volume of 0.5ml has been associated with a lower incidence of inadvertent injectate spread (Manchikanti *et al.* 2012)[16]. The rate of false positives is most often cited between 15 and 40%, due to factors such as placebo response, use of sedation, and excessive use of local anaesthesia. We will aim to minimise this by not using sedation and by limiting the local anaesthetic volume to 0.5ml per nerve block.

There is currently no justification for double, comparative blocks as these are associated with a significant false-negative rate and are not shown to be cost-effective (Bodguk and Holmes 2000)[17].

4. Investigational medicinal product

4.1. List and definition of each IMP, including placebos

4.1.1. IMPs

1. Methylprednisolone acetate BP 40mg/ml, as Depo-Medrone 40mg/ml
2. Bupivacaine hydrochloride BP 0.5%

4.1.2. Non-IMPs

1. Lidocaine hydrochloride injection BP 1% w/v, solution for injection.

For the diagnostic injections, participants will receive 0.5ml 1% lidocaine per injection. Six injections will be given i.e. a maximum of 3ml 1% lidocaine.
The NIMP will be taken from hospital stock.

4.1.3. Placebo

1. Sodium chloride 0.9% intravenous infusion BP ('normal saline')

The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone.

The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.

The sham group will receive normal saline 0.9% 0.5ml.

4.2. Formulation of IMP.

Methylprednisolone acetate BP 40mg/ml in a sterile, aqueous suspension, as Depo-Medrone 40mg/ml.

Bupivacaine hydrochloride BP 0.5%, solution for injection.

Normal saline 0.9% 5ml per vial.

4.3. IMP supply

All the IMPs, and placebo will be supplied by individual site NHS Trust pharmacies. The injections and IMPs used form part of routine NHS care.
This is a Type A study, following assessment the IMP will be stored and dispensed as per NHS site local procedure.

4.4. Prescription of IMP

The Sponsor will provide each site with a trial-specific administration chart template (includes prescription). Should any site wish to use their own template, this will first be reviewed by the Sponsor.

The site Principal Investigator will prescribe the IMPs.

4.5. Preparation and administration of IMP

The IMPs will be prepared and administered by each site's Principal Investigator or other unblinded delegate. See sections 1.2.1 (facet joint injections) and 1.2.2 (sham procedure) for further details.

Study medications will be stored within each NHS site as per their local procedures for this drug and procedure. No additional monitoring or checks will be performed.

4.6. Packaging and labeling of IMPs

As IMPs will be used as per local practice within a theatre setting, these will not be labelled. The IMP will be handled according to local NHS site procedures only.

4.7. Receipt /storage and handling/accountability of IMP

IMPs will be received, stored, dispensed and will be handled according to Local NHS site procedures only

Facet Joint Trial administration (Blinded) form should be used to document amount of IMP used, batch numbers and expiry dates.

4.8. IMP stability

Site pharmacies will be responsible for dispensing in line with their local dispensing procedures and excursion management normal practices.

4.9. Prior and concomitant therapies

Any medication other than the study medication taken during the study will be recorded in the CRF. There are no specific medication contraindications.

4.10. Dose modification/reduction/delay

No dose modification/reduction/delay is permitted within the study.

4.11. Return/recall or destruction of IMP

Local recall procedures will be used for recalls. Any IMP remaining following a procedure will be destroyed as per local procedure within theatres.

5. Study procedures

5.1. Recruitment

The feasibility study will be conducted in three hospital-based pain medicine centres: Barts Health NHS Trust), Basildon and Thurrock University Hospitals NHS Foundation Trust, and The Walton Centre NHS Foundation Trust. The study will be recruiting from hospital based pain, spinal and musculoskeletal clinics, this can include associated community based clinics within the same NHS trusts.

5.1.1. Informed consent procedures

Potential participants will initially be given a copy of the participant information sheet and given a verbal explanation of its contents. This will include details on the nature of the study, the implications and constraints of the study protocol, and any known side effects and risks involved in taking part in the study. Participants will be told that they are free to withdraw from the study at any time for any reason, without prejudice to future care or obligation to give the reason for withdrawal. They will be given as much time as they wish to consider the information, and to ask questions.

A medically qualified and experienced investigator (Principal Investigator or a medically qualified person within the research team with authority given by the site Principal Investigator, documented on the site delegation log) will obtain written informed consent. Participants will be expected to sign and date the form to indicate their consent. The original signed form will be retained at the study site, and a copy given to the participant and a copy in the site medical records.

Prior to any study-specific procedures being carried out, participants will sign and date the latest approved version of the informed consent form.

5.2. Screening procedures

The diagnostic test used for facet-joint disease is a positive response to medial branch nerve blocks. The rationale for this is detailed in section 3.5.

Diagnostic medial branch nerve blocks will be carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

Patients with a positive response (pain is likely to be of facet-joint origin) are considered eligible to be

randomised to receive either the facet-joint injection or sham procedure.

5.3. Randomisation procedures

Eligible and consented participants will be individually randomised in a 1:1 ratio to receive either the facet-joint injection (intervention group) or a sham (placebo injection) procedure (control group). Both intervention and control patients will receive a combined physical and psychological programme (CPP) after their injections. Patients will be allocated to intervention and control and minimisation used to ensure between group balance by centre and baseline pain scores. The allocation sequence will be computer-generated and to ensure concealment, will be provided through a password protected web-based portal. The randomisation procedure will be developed and maintained by the Peninsula Clinical Trials Unit (PenCTU), a United Kingdom Clinical Research Collaboration (UKCRC) accredited unit.

5.4. Schedule of assessment

Visit 1	Screening and informed consent. Outcome questionnaires at baseline.
Visit 2	Diagnostic test (medial branch nerve blocks).
Visit 3	FJIs or sham procedure.
Visit 4	Outcome questionnaires at 6 weeks.
Visit 5	Outcome questionnaires at 3 months.
Visit 6	Outcome questionnaires at 6 months.

There will be 6 study visits in total – 3 visits are part of routine clinical practice (patients are seen in the pain clinic, referred for FJIs, then followed-up at 6 to 8 weeks), and 3 visits are additional. We anticipate that it will take up to one hour to complete the set of outcome questionnaires. The outcome questionnaire visits will take place in research nurse-led clinics. As detailed in the table below, adverse events will be assessed for at every visit by a blinded sub-investigator.

	Pre-screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
					6 weeks after injections +/- 2 weeks	3 months after injections +/- 2 weeks	6 months after injections +/- 2 weeks
Informed consent		x					
Targeted physical examination	x	x					
Inclusion/exclusion criteria fulfilled		x	x	x	x	x	x
Medical history recorded		x					
Demographic data recorded		x					
Drug history recorded		x	x	x	x	x	x
Breakthrough analgesia recorded				x	x	x	x
Adverse events			x	x	x	x	x
Outcome questionnaires:		x			x	x	x
Expectation of benefit scale		x					
Brief Pain Inventory (Short Form)		x			x	x	x
Short-form McGill Pain Questionnaire (SF-MPQ-2)		x			x	x	x
EQ-5D-5L		x			x	x	x
12-item Short Form Health Survey (SF-12)		x			x	x	x
Oswestry Low Back Pain Disability Questionnaire		x			x	x	x
Pain Self Efficacy Questionnaire (PSEQ)		x			x	x	x
Hospital Anxiety and		x			x	x	x

Depression Score (HADS)							
Pain Catastrophizing Scale (PCS)		x			x	x	x
Stanford Presenteeism Scale		x			x	x	x
Satisfaction with treatment scale					x	x	x

5.5. Follow up procedures

Participants will be complete the study 6 months following their active or sham treatment. Following completion, patients will be followed up by the pain clinics as per routine NHS practice, within the standard NHS timeframe.

5.6. Study evaluations

All the study evaluations will be carried out by blinded research team members at each of the three sites e.g. a medically-trained clinical research fellow or research nurse.

The following assessment tools will be used in the study:

1. Pain intensity and characteristics: Brief Pain Inventory (BPI) (Short Form) Modified, with its 11-point NRS Short Form McGill Pain Questionnaire.

2. Use of co-analgesics in the previous week: participant self report.

3. Lack of efficacy in pain relief, or for side effects: early withdrawal from the study.

4. Expectation of benefit (asked at baseline only): 0 to 6 scale, ranging from "expect no improvement" to "expect total improvement".

5. Health-related quality of life: EQ5D-5L, 12-item Short Form Survey (SF-12).

6. Functional impairment: Oswestry Low Back Pain Disability Questionnaire, Pain Self Efficacy Questionnaire (PSEQ).

7. Satisfaction with treatment (after treatment given): numerical rating scale (NRS) from 0 to 10 (0 = extremely dissatisfied, 10 = extremely satisfied).

8. Complications and adverse events. These will be the subjects of enquiry at visits and following procedures, as well as through spontaneous reporting at any time. They will be acted upon as necessary, and for the patient's benefit, and fully documented in the clinical research form and the hospital notes.

9. Co-psychological well-being: Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, SF-12, BPI.

10. Healthcare utilisation and costs, and impact on productivity. This will include the use if published national costs to calculate costs of delivering each treatment arm/intervention and downstream healthcare utilization. The tools to assess this are the Stanford Presenteeism Scale 6, self-reported measures of sickness absence over the previous 3 months, and healthcare utilisation in the form of hospital visits, treatments and medications. This data will be collected at each outcome visit in the case report form.

5.7. End of study definition

The study will be completed when all randomised patients have completed the final follow-up assessments.

5.8. Procedures for unblinding

Unblinding can only be undertaken by an authorised person who is documented on the site delegation log. In the event of an emergency, the investigator will decide the necessity of unblinding the subject's treatment assignment. The unblinding procedure will be carried out by the PI at each site, following the 'unblinding procedure' SOP.

If unblinding occurs, the investigator must record the reason for unblinding on the case report form, as well as the date and time of the event.

The Principal Investigators are not blinded and will be informed if this is deemed necessary by the sub-investigators. Please see section 6.8 for details of reporting SUSARs.

5.9. Subject withdrawal

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Pregnancy (see section 6.10)
- Ineligibility (arising during the study)
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn from treatment but continue in the study
- Consent withdrawn from study
- Lost to follow up

The reason for withdrawal will be recorded in the CRF.

5.10. Data collection and follow up for withdrawn subjects

If a patient wishes to withdraw from the study all identifiable data collected will be removed and excluded in the analysis. Data that is not identifiable by the research team will be retained.

6. Pharmacovigilance

6.1. General definitions

6.1.1. Adverse event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an Investigational Medicinal Product (IMP), **whether or not considered related to the IMP**.

6.1.2. Adverse reaction (AR)

An AR is any untoward and unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

6.1.3. Serious adverse event (SAE) or serious adverse reaction (SAR)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

An SAR is an adverse reaction that is classed as serious and which <u>is consistent</u> with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC).

6.1.4. Suspected unexpected serious adverse reaction (SUSAR)

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the Summary of Product Characteristics (SmPC).

6.2. Reference safety information

The safety information, including the incidence of predicted undesirable side effects for each of the IMPs can be found in their Summary of Product Characteristics (section 4.8 'Undesirable effects').

6.3. Investigators assessment

6.3.1. Seriousness

Each site will have a sub-investigator who will be delegated the task of assessing whether the event is serious according to the definitions given in section 6.1. The Principal Investigator responsible for the care of the patient is not blinded and their involvement will affect the bias of the study.

6.3.2. Causality

The Principal Investigator must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

6.3.3. Expectedness

The Principal Investigator must assess the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

6.3.4. Severity

The investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

6.4. Notification and reporting adverse events or reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes and the CRF.

6.5. Notification and reporting of serious adverse events/SUSAR

All serious adverse events (SAEs) will be recorded in the subjects' notes, the CRF, the Sponsor SAE form and reported to the Joint Research Management Office (JRMO) within 24 hours of the PI or co-investigators becoming aware of the event. For all SAEs the Chief Investigator will act as Sponsor's medical representative and assess the event. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site.

Suspected unexpected serious adverse reactions (SUSARs) that occur during the trial will be reported to the JRMO within 24 hours of the Principal Investigator becoming aware of the event. SUSARs should be reported to the Sponsor within 24 hours as the Sponsor has a legal obligation to report this to the MHRA within 7 days (for fatal or life-threatening SUSARs) or 15 days for all other SUSARs.

The PI will need to complete the CIOMS form in conjunction with the Sponsor SAE form to be sent to the MHRA by the Sponsor. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

The original and any subsequent follow up of Serious Adverse Event forms and CIOMS forms (where applicable), together with the fax confirmation sheet must be kept with the TMF at the study site.

6.6. Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the Sponsor, main Research Ethics Committee (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event **immediately**.

The CI has an obligation to inform both the MHRA and Main Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The Sponsor (JRMO) should be made of the USM prior to implementation where possible but must be sent a copy of the correspondence with regards to this matter prior to its submission to Regulatory authorities.

6.7. Annual safety reporting

The DSUR will be created by the CI, and once reviewed and approved by the Sponsor, will be sent to the REC and MHRA (the date of the anniversary is the date on the "notice of acceptance letter" from the MHRA) using Sponsor template. The CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial.

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the REC "favourable opinion" letter from the MREC) and to the Sponsor.

6.8. Procedures for reporting blinded SUSARs

As this is a blinded study, the treatment code may be broken once a SUSAR is reported. The JRMO will report the SUSAR to the Principal Investigator, who is not blinded. The Principal Investigator will assess each case for seriousness, expectedness and causal relationship as if it was the tested IMP that caused the reaction. If the case appears to be a SUSAR then it should be unblinded and the following considered:

If the administered product is the tested IMP (facet-joint injections with bupivacaine and methylprednisolone) this will be reported as a SUSAR to the MHRA, the research ethics committee and IMP provider within the timelines outlined in section 6.5.

If the administered product is the sham procedure (peri-articular normal saline) the adverse reaction will be reassessed for expectedness according to the study protocol. If the adverse reaction is unexpected then the SUSAR will be reported; otherwise it is an expected serious adverse reaction that will be reported to the Sponsor within 24 hours.

6.9. Overview of the safety reporting process/pharmacoviligance responsibilities

The Chief Investigator has the overall pharmacovigilance oversight responsibility. The CI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the Sponsor's requirements.

6.10. Pregnancy

Verbal confirmation will be obtained at screening to ascertain if the patient is pregnant or not, pregnant participants will not be enrolled into the study. Prior to each interventional procedure involving X-rays, local hospital procedures will be followed to confirm if female participants are pregnant.
If a patient becomes pregnant whilst involved in a CTIMP, it is considered to be an AE of special interest and will be reported to the Sponsor within 24 hours of the Principal Investigator becoming aware. The Sponsor pregnancy form will be used, reported in the same way as a SAE, and the patient will be prematurely withdrawn from the study.

The Principal Investigator will also follow up the pregnancy until delivery as well as monitoring the development of the newborn for the 28 days after birth. Any events that occur during this time that could be considered to be a SAE must be reported to the Sponsor in line with sections 6.4 and 6.5, utilising the Sponsor SAE reporting form.

7. Statistical considerations

7.1. Feasibility outcomes

1. Patient flow – participant flow through the trial will be summarised using the CONSORT diagram and will reflect numbers of patients screened, consented, randomised, receiving intervention, and completed outcomes.

2. Patient recruitment and retention rates – we will calculate the ratio of the number of patients screened: recruited and time to achievement of patient recruitment target by each centre.

3. Acceptability of trial methods to patients and clinicians.

4. Fidelity of blinding – we will calculate the proportion of correct guesses of patient assignment by patients and research staff at each follow up.

5. Delivery of co-interventions – we will assess the consistency of CPP delivery across the three centres by on-site visits by the trial lead physiotherapist.

7.2. Sample size

A total of 60 patients will be recruited and randomly and equally allocated to either intervention and control groups. Assuming a 20% attrition rate, 24 full data sets per arm will be completed at the end of the study. This sample size will allow us to achieve our various feasibility objectives. For example, 60 patients gives the ability to estimate the precision of our assumed attrition rate with error of error of ±5% at 95% confidence level and 24 patients per arm is acceptable for a reasonable estimate of variance of outcomes (Browne 1995)[18].

To predict the sample size for the main trial we have made the following assumptions for the pain intensity scores: for a pain NRS (0-10), IMMPACT propose a clinically important minimal difference of 2 points (Dworkin *et al.* 2005)[19]. Based on a typical pain NRS standard deviation of 3.0 to 4.0 seen in previous chronic pain trials, at 90% power and 5% alpha, a two-arm superiority trial would require a total of 100 to 160 complete patient data sets.

From 1000 new patient attendances at the pain clinics with low back pain, it is expected that approximately 1 in 4 patients to be eligible to enter the study. This is based on clinical experience and published studies based on responses to controlled diagnostic facet-joint injections performed in accordance with the criteria established by the International Association for the study of pain (Dworkin *et al.* 2005)[19]. Of these 250 patients, approximately 60% will consent to enter the study.

Following diagnostic medial branch nerve blocks, we would expect approximately 40% patients to have a positive response (Cohen *et al.* 2010 and Van Zundert *et al.* 2010)[20, 21]. These 60 patients will be randomised to the two groups, with a estimated maximum of 1 in 3 patients dropping out over study period. This estimation is based on the clinical experience of the Principal Investigators.

7.3. Statistical analysis

As this is a feasibility study, it is not proposed to formally inferentially test differences in outcomes or costs between or within the groups. Recruitment and attrition rates will be calculated with 95% confidence intervals. The study will report mean and standard deviations for primary and secondary outcomes for the two groups at baseline and all follow-up visits.

8. Data handling and record keeping

8.1. Confidentiality

Patients will be aware from the informed consent process that Sponsor, monitors and regulators will require direct access to all study information but that their privacy and confidentiality will be protected.

The Peninsula CTU has established procedures to ensure that patients' private information and trial data are protected. Web-based methods of randomisation and concealment are password-protected. The electronic database is kept on a secure, password-protected server allowing access to only the Peninsula CTU programming team and the Plymouth University database support team. All communication (data transferred) between the website and database is encrypted. The database is encrypted before it is transferred to the backup storage location.

Patient data will be protected in secured storage areas and patients' names and identifying information will be maintained separately from case report forms.

The Principal Investigator as well as the study team will adhere to these parameters to ensure that the patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, each patient, at time of consent must be allocated a unique screening number by either the PI or a member of the study team before undergoing any screening procedures. The patient's initials (the first letter of their first name and the first letter of their last name) will be used as a means of pseudo-anonymising parameters. This information will be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled onto the study, the patient will be allocated a randomisation number by the PI.

If any patient information needs to be sent to a third party (including correspondence/communication to central laboratories, CROs, Sponsor) the PI and the study team should adhere to patient pseudo-anonymous parameters. This includes the patient initials, date of birth, gender as well as the unique study ID/randomisation number. Any information that is to be collected by these third parties will utilise these coded details for any relevant documents as well as maintaining databases.

No identifiable information will be collected from the subjects. Only members of the research team will have access to the information. The Principal Investigators will be the custodians of the data. No patient details will be transferred outside the EU. The subjects will be anonymised with regards to any future publications relating to this study.

8.2. Case report form

The case report form will be printed as a paper document and supplied for each study participant.

8.3. Record retention and archiving

During the course of research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research trial is complete, it is a requirement of the Sponsor that the records are kept for a further 20 years. Coordination documents and the TMF will be archived with in the Barts Health NHS Trust Modern Records Centre, as per Sponsor policy. Site files from other sites must be archived at that external site, for 20 years.

8.4. Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and 2008, Sponsor's policies and procedures and any subsequent amendments.

8.5. Clinical governance issues

8.5.1. Ethical considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient and any advertising material will be submitted by the Chief Investigator to an independent Research Ethics Committee.

Informed consent

The Principal Investigator or a medically qualified person within the research team on the site delegation log, who has completed a Good Clinical Practice course and is knowledgeable about the study and able to competently answer questions, will carry out the informed consent process. Written informed consent will be obtained with approval of the local ethics committee and in accordance with the Declaration of Helsinki. We will not recruit potentially vulnerable patients to the study.

Patients will be fully knowledgeable about the purpose and potential benefits and risks of the study. They will be made aware that they may not directly benefit themselves, but the results of the study could benefit future patients. They will have the right to withdraw from the study at any stage. Patients will be made fully aware of any potential complications of the diagnostic medial branch nerve block, FJIs and sham procedure. The most prevalent complication of diagnostic medial branch nerve blocks is temporary paraesthesia and loss of motor function in the legs from overflow of local anaesthetic (van Kleef *et al.* 2010)[6]. This risk will be minimised by limiting the concentration and volume of local anaesthetic and precise X-ray guided needle placement. One recent prospective non-randomised study of patients undergoing facet-joint nerve blocks concluded that major complications are extremely rare (Manchikanti *et al.* 2012)[16], whereas minor side effects such as localised bruising and bleeding are common.

Ethical considerations of the sham procedure

The Principal Investigators feel that the use of a sham procedure can be ethically justified despite the potential risk to study participants, as it will enable a valuable, clinical question to be answered by the research (Horng and Miller 2003)[22]. The sham procedure itself is methodologically necessary to test the study hypothesis and will allow a better evaluation of the procedure than comparing FJIs against no treatment. During the informed consent process patients will be made aware that they may be administered a sham procedure instead of FJIs. All risks to study participants have been minimised where possible e.g. no systemic steroid administration. The risks of ionising radiation for the sham procedure has been assessed by medical physics experts and is considered a minor level of risk, comparable to about 2 months of background exposure. The Principal Investigators believe that the risks of using ionising radiation to correctly site the needle outweigh the potential significant complications such as dural puncture, spinal cord trauma, intravascular injection and neural trauma.

8.6. Quality control and quality assurance

8.6.1. Summary monitoring plan

Please see agreed monitoring plan for full details. On-site monitoring will occur for this study by an experienced monitor every 4 to 6 months. This will include but not be limited to an investigator site file review, source data verification, pharmacy file and accountability review.

8.6.2. Audit and inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation (e.g. MHRA).

Internal audits will be conducted by a Sponsor's representative

8.7. Serious breaches in GCP or the trial protocol

The Sponsor of the clinical trial is responsible for notifying the licensing authority and REC in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to the trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a 'serious breach', is a breach which is likely to effect to a significant degree:

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

The CI is responsible for reporting any serious breaches to the Sponsor (JRMO) **within 24 hours**.

8.8. Non-compliance

Non-compliances will be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The site and coordinating team will maintain a log of the non-compliances and deviations to ascertain if there are any trends developing which to be escalated. The Sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. If the actions are not dealt with accordingly, the JRMO will agree an appropriate action, including an on-site audit and if appropriate withdrawal of the study.

9. Trial committees

A trial manager has been appointed to work alongside the Chief Investigator to coordinate and oversee the overall management of the trial.

To ensure appropriate project management and governance, we will establish the following groups which will meet at least annually:

9.1. Trial Management Group (TMG)

The TMG is responsible for the overall management of the project and will comprise of all co-applicants and members of the study research team. Given the dispersed nature of the three clinical sites, meetings may take place via tele- and videoconference. Primary care general practices will be made aware of the proposed trial at the three sites, and will be invited to join the TMG.

9.2. Trial Steering Committee (TSC)

The TSC will provide independent advice and support to the trial and report to the funder on trial progress. The TSC will be chaired by an independent clinician with experience of pain trials.

9.3. Data Monitoring Committee (DMC)

The DMC will have access to unblinded data, and will make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. It has independent members who are all experts in pain medicine.

10. Publication policy

The results may be published and/or presented at scientific meetings. All manuscripts and abstracts, which refer to data originating from the trial, must be submitted to the Sponsor before publication. The Sponsor has the right to refuse the results for registration purposes, internal presentation and promotion.

The findings of the project will be reported to meet the needs of different audiences and will include presentation at relevant national and international conferences, and submission for publication to peer-reviewed academic journals. Although the copyright will be assigned to the publisher, we would with permission ensure that the top-line results will be available in the public domain, such as on the public access area of the British Pain Society website.

A short plain English language summary of the main research findings will be distributed to study participants, primary care practices and the local Clinical Commissioning Groups, and lay interested parties, including the charity BackCare. The lay summary will also be sent to relevant local and national self-help groups and charities with an interest in the management of low back pain. Depending on the findings, there may be a review of the evidence-based pain patient pathways currently in development with Map of Medicine, and any future NICE guidelines and Quality Standards in this field.

The feasibility study would not yield a definitive outcome, but a qualitative report may be deliverable. The full study would be disseminated as presentations at scientific meetings and peer-reviewed publications. Depending on the results of the definitive trial, the cost-effectiveness of facet-joint injections will either be positive and hence potentially supported in patient care pathways, or not recommended for routine clinical practice. The new evidence would inform future guideline developments by NICE or other guideline development groups and would likely be featured in future review articles on the management of pain, and also ultimately inform patient care pathways.

11. Patient and public involvement

Patients with personal experience of low back pain have collaborated in the early stages of study design, for example in advising on the acceptability of study visits and outcome questionnaires. The outcome questionnaires have been tested on patients presenting to the multidisciplinary pain clinic. Patient representatives will be invited to attend the trial steering committee meetings. The public will be involved in dissemination of results, by making use of personal networks to publicise study findings.

11.1. Remuneration

Patients will not receive monetary compensation for taking part in the study, but they will receive prompt reimbursement of travel expenses.

12. References

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