Health Technology Assessment Programme

National Institute for Health Research

NIHR HTA Programme

13 February 2014

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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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/Acronym: **Facet-joint feasibility study**

Sponsor: Barts Health NHS Trust

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REC reference: Insert once known

EudraCT reference: Insert once known

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**, 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.

Chief Investigator Name:
Professor Richard Langford

Chief Investigator Site:
Barts Health NHS Trust

Signature and Date:

Statistician Agreement Page

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**, 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.

Statistician Name: Professor Rod Taylor

Site: University of Exeter

Signature and Date:

Principal Investigator Agreement Page

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Principal Investigator Name: Dr Vivek Mehta

Principal Investigator Site: Barts Health NHS Trust

Signature and Date:

Principal Investigator Name: Dr Simon Thomson

Principal Investigator Site: Basildon & Thurrock NHS Foundation Trust

Signature and Date:

Principal Investigator Name: Dr Manohar Sharma

Principal Investigator Site: The Walton Centre NHS Foundation Trust

Signature and Date:

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
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MOH	Medication-overuse headache
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle 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

Index

1. Introduction

1.1 Background and rationale

Pain of lumbar facet-joint origin is a common cause of low back pain in adults[2], 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[5]. 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[6]. 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[7].

Due to the lack of high quality, robust clinical evidence the National Institute for Clinical Excellence (NICE) guidelines published in 2009 did recommend injections of therapeutic substances into the back for nonspecific low back pain[2], 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[8]. 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[9, 10, 11].

As there is no widely accepted consensus on the technique of facet-joint injections (FJIs) and sham procedure, we 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, volume of injection and use of fluoroscopy 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[6]. 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 to 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 we optimise patient selection criteria, using clinical and investigative diagnostic methods?

2. Can we determine and standardise the method of injection and establish an appropriate sham procedure?

3. Can we deliver justification for further studies to evaluate treatment methods to target and attenuate he source of chronic LBP of facet-joint origin?

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

5. Can we recruit and retain sufficient patients?

1.2 Health technologies being assessed

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

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 theatre protocols with regards to admission and discharge criteria.

1.2.1. Facet-joint injections

Method. A spinal needle will be placed within the facet-joint under fluoroscopic 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 anaesthetic 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 injection of radio-opaque contrast and visualisation of the needle position within the joint space, and local anaesthetic 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 fluoroscopic 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.

Notes. Para-spinal tenderness will be elicited as before (section 5.5.1), and the needle inserted under fluoroscopic 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

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[1]. We searched the MEDLINE database (1966 to October 2012) and checked the reference list of identified articles for any additional papers.

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 we can demonstrate successful standardisation of the method of injection and the test-run of the sham procedure, and that the proposed study design is deemed acceptable by patients and clinicians, and we 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).

a. by assessing the feasibility of recruitment in the three centres, with regards to a potential definitive trial, by reviewing the number of completed patient data sets, auditing the quality of data entry at the centres, 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 double blind two-arm randomised controlled study. Patients with non-specific low back pain of three months' duration or longer, 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.

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2.3 Trial duration

We anticipate that the project will take a total of 21 months to complete. We will start preparation for the study with protocol refinement, statutory and regulatory requirements, preparation of study documentation, recruitment and training of staff, and promotion of the study in clinics. We will identify and recruit patients (months 0 to 6), carry out study procedures (months 0 to 18) and collect outcome data (months 0 to 18). There will be ongoing data coding, entry and cleaning (months 0 to 18), with data analysis, report writing and dissemination of results (months 18 to 21).

2.4 Study scheme diagram

The study scheme diagram will be attached as a separate document.

3. Subject Selection

3.1 Number of subjects and subject selection

Patients will be recruited from pain clinics at the three participating NHS centres and their associated community based pain clinics. Patients will be referred by their general practitioners 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.

3.2 Inclusion criteria

1. Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of nonspecific low back pain
2. Low back pain of greater than three months' duration
3. Average pain intensity score of 4/10 or more in the seven days preceding recruitment despite NICE recommended treatment.[2]
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.[2]

3.3 Exclusion criteria

1. Patient refusal.
2. More than four painful lumbar facet-joints.
3. Patient has not completed at least two components of NICE-recommended best non-invasive care.[2]
4. 'Red flag' signs
5. Hypersensitivity to study medications or X-ray contrast medium.
6. Radicular pain.
7. Dominantly midline tenderness over the lumbar spine.
8. Any other dominant pain.
9. Any major systemic disease or mental health illness that may affect the patient's pain, disability and/or their ability to exercise and rehabilitate.
10. Any active neoplastic disease, including primary or secondary neoplasm.
11. Pregnant or breastfeeding patients.
12. Previous lumbar facet-joint injections.
13. Previous lumbar spinal surgery.
14. Patients with morbid obesity (body mass index of 35 or greater).
15. Major trauma or infection to the lumbar spine.
16. Participation in another clinical trial in the past thirty days.
17. Patients unable to commit to the six-month study duration.
18. Patients involved in legal actions or employment tribunals related to their low back pain.
19. Patients with a history of substance abuse.

3.4 Diagnostic test

Method. Diagnostic medial branch nerve blocks will be carried out at each painful level with fluoroscopic 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 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[9]. A volume of 0.5ml has been associated with a lower incidence of inadvertent injectate spread[14]. 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[15].

4. Investigational Medicinal Product

4.1 Facet-joint injections

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

4.2 Sham procedure

Method. A spinal needle will be placed in the peri-articular space surrounding the facet-joint under fluoroscopic 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.

4.3 List and definition of each IMP, including placebos

Active group. Methylprednisolone 20 mg injected per joint.
Sham group. Normal saline 0.5 ml.

4.4 Formulation of IMP

Methylprednisolone 40 mg per vial.
Normal saline 0.9% 5 ml per vial.

4.5 IMP supply

Methylprednisolone (40mg vial, Pfizer) and normal saline 0.9% (5 ml vial) will be provided by Barts Health NHS Trust Pharmacy.

4.6 Prescription of IMP

Barts Health NHS Trust Pharmacy will be provided with the name and details of prescribing healthcare professionals involved in the study, via a current site delegation log. This is to ensure that the study IMPs will only be dispensed if prescribed by these named individuals.

4.7 Preparation and administration of IMP

Facet-joint injections

Method. A spinal needle will be placed within the facet-joint under fluoroscopic 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 anaesthetic and steroid to other potential pain-generating structures.

Study medications will be stored at their recommended temperatures (according to the product information leaflets) in a dry place, protected from light. The storage areas at each of the trial sites will be monitored and maintained by trial staff.

4.8 Packaging and labelling of IMPs

IMPs will be packaged and labelled in accordance with Annex 13 (Manufacture of Investigational Medicinal Products).

4.9 Accountability/receipt /storage and handling of IMP

IMPs will be received, stored and accounted for in accordance with Annex 13 (Manufacture of Investigational Medicinal Products). We do not anticipate the need for freezers or large storage containers.

4.10 Dispensing of IMP

SOPs will be in place in place within each pharmacy for dispensing the IMP. Each member of staff dispensing the IMP will sign the local pharmacy dispensing log to document appropriate IMP tracking. Members of the trial team will have had study specific training and their involvement will be documented in the study specific trial delegation log.

4.11 IMP stability

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

4.12 Prior and concomitant therapies

Any medication, other than the study medication taken during the study will be recorded in the CRF.

4.13 Dose modification/reduction/ delay

This is not applicable to the study.

4.14 Return/recall or destruction of IMP

IMPs to be destroyed will be documented and accounted for in accountability/drug destruction logs.

5. Study Procedures

5.1 Recruitment

The feasibility study will be conducted in three hospital-based pain medicine centres: Barts Health NHS Trust (until April 2012, Barts and The London NHS Trust), Basildon and Thurrock University Hospitals NHS Foundation Trust, and The Walton Centre NHS Foundation Trust. We will be recruiting from hospital based pain clinics and their associated community based pain clinics

5.2 Informed consent procedures

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

Potential participants will initially be given a copy of the patient information leaflet 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 suitably qualified and experienced investigator will obtain written informed consent, with authority given by the Chief/Principal Investigator. 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.

5.3 Screening procedures

Diagnostic test

Method. Diagnostic medial branch nerve blocks will be carried out at each painful level with fluoroscopic 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 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[9]. A volume of 0.5ml has been associated with a lower incidence of inadvertent injectate spread[14]. 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[15].

5.4 Randomisation procedures

This feasibility study is double blind two-arm randomised controlled study. Patients with non-specific low back pain of three months' duration or longer, 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. 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.

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice. Any amendments to the protocol will be submitted to the REC for approval as appropriate.

5.5 Schedule of treatment for each visit

Participants for the study will be sent an invitation letter and information leaflet and will be asked to contact the study centre if they are interested in taking part. They will be screened for eligibility by telephone or in person and then provided with the consent forms to consider their participation. They will have as long as they need to make an informed decision and will be able to discuss their participation prior to their appointment with the study staff. Primary and secondary outcomes will be collected at 4 time points: baseline (pre-randomisation), and at 6 weeks, 3 months and 6 months post-randomisation. In addition, patient demographic data (e.g. age, gender, duration of chronic pain) will collected at baseline. Data will be collected by an independent member of the research team, blinded to patient allocation.

5.6 Schedule of assessment

Visit 1 Screening and informed consent. Outcome questionnaires at baseline.
Visit 2 Diagnostic test.
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 a research nurse-led clinics.

5.7 Follow-up procedures

Participants will be complete the study 6 months following their active or sham treatment. The patients would be followed up by the pain clinics as per routine NHS practice after completion of study.

5.8 Study evaluations

Assessment tools/notes

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
3. Early withdrawal from the study for lack of efficacy in pain relief, or for side effects
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-L, 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)
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 for later analysis.
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: Published national costs to calculate costs of delivering each treatment arm/intervention and downstream healthcare utilization, Stanford Presenteeism Scale 6 Self-reported measures of sickness absence over the previous 3 months. Text message/telephone follow-up to assess healthcare utilisation. This is to ensure comprehension and up-to-date data collection

5.9 Laboratory assessments

Laboratory assessments are not required in this study.

5.10 End of study definition

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

5.11 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 blinded treatment assignments will be accessible to the investigator should a subject need to be unblinded in an emergency using the unblinding envelopes. If unblinding occurs, the investigator must record the reason for unblinding, as well as the date and time of the event. Corresponding information will be recorded on the CRF by the investigator.

5.12 Subject withdrawal

Each participant has the right to withdraw 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
- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- 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.

5.13 Data collection and follow up for withdrawn subjects

The patients and all identifiable data collected will be withdrawn from the study and excluded in the analysis. Data that is not identifiable by the research team will be retained.

6. Laboratories

This section is not applicable to the study.

6.6 Data Recording/Reporting

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principle, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

7. Pharmacovigilance

7.1 General definitions

7.1.1 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**.

7.1.2 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.

7.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Serious Adverse Reaction (SAR)

An SAR is an adverse reaction that is classed as serious and which is consistent with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB) for that product.

7.1.3 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) or Investigator's Brochure (IB) for that product.

7.2 Investigators assessment

7.2.1 Seriousness

The Chief/Principal Investigator responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 7.1.

7.2.2 Causality

The 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.

7.2.3 Expectedness

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

7.2.4 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

7.3 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 (where appropriate) and the CRF.

7.4 Notification and reporting of Serious Adverse Events/SUSAR

7.4.1 All Serious Adverse Event (SAEs) will be recorded in the subjects’ notes, the CRF, the sponsor SAE form and reported to the Joint Research and Development Office (JRO)/ IMP provider (if applicable) within 24 hours of the CI or PI or co-investigators becoming aware of the event. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites. Please ensure that the sponsor has been informed of these nominated co-investigators.

7.4.2 Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the JRO/ main REC/IMP provider (if applicable) within 24 hours of the CI or co-investigator becoming aware of the event. SUSARs should be reported to the sponsor (JRO Office) 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. In the case of multicentre studies, the PI or the co-investigators at the participating site must inform the CI within 24 hours of the event. The CI or co-investigators at the co-ordinating site must inform the sponsor (JRO) immediately to allow reporting to the MHRA within the allocated timelines. The CI 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.

7.5 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 (JRO) must be sent a copy of the correspondence with regards to this matter.

7.6 Annual safety reporting

The Annual Safety Reports (ASR) will be sent by the CI to the sponsor, the MREC and MHRA (the date of the anniversary is the date on the “notice of acceptance letter” from the MHRA) using the ASR form. 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 MREC "favourable opinion" letter from the MREC) and to the sponsor.

7.7 Procedures for reporting blinded SUSARs

In the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of a SUSAR. However, the blind should be maintained, where possible and appropriate, for staff that are involved in data analysis and interpretation. It is the allocated responsibility of the CI by the sponsor for pharmacoviligance management and reporting. In this instance, an allocated unblinded individual (s), with no involvement in data management of the study should be responsible for the unblinding event. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

It is recommended that in the case of a blinded study, the case is assessed 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, the case would be reported as a SUSAR to the MHRA/ appropriate Main Research Ethics Committee/IMP provider (if applicable) within the timelines outlined in section 7.4.2.

If the administered product is a comparator with a marketing authorisation, the adverse reaction should be reassessed for expectedness according to the study protocol. If the adverse reaction is unexpected then the SUSAR should be reported; otherwise it is an expected serious adverse reaction which still requires reporting to the sponsor/IMP provider (if applicable) within 24 hours.

7.8 Overview of the safety reporting process/pharmacoviligance responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements. SOPs would be put in place to ensure that all SAE/SUSAR reporting is conducted in accordance with the sponsor's timelines.

7.9 Pregnancy

If a patient becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires monitoring and follow up. If a patient, or his partner,

becomes pregnant whilst enrolled in a CTIMP in which the foetus has been exposed to an investigational medicinal product, immediate reporting to the sponsor is required (within one working day of the PI/CI becoming aware of the event) using a JRO pregnancy template form. The CI/PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The patient will be prematurely withdrawn from the study.

The PI/CI also must follow up the pregnancy until delivery as well as monitoring the development of the newborn for the appropriate time (please indicate for this IMP) 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 section 7.4.1, utilising the sponsor SAE reporting form.

8. Statistical Considerations

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.

8.1 Endpoint efficacy analyses

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 and acupuncture delivery across the three centres. Details of therapy received by each patient will be collected as part of the clinical research form at each follow up visit.

8.2 Sample size

We will recruit a total of 60 patients and randomly and equally allocate them to either intervention and control groups. Assuming a 20% attrition rate, we have 24 complete data sets per arm 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 [20]. 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[3]. 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, we expect approximately 1 in 4 patients to be eligible to enter the study. This is based on our 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 pain3. 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[21, 22.] These 60 patients will be randomised to the two groups, with a maximum of 1 in 3 patients dropping out over study period.

8.5 Statistical 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.

9. Data Handling & Record Keeping

9.1 Confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The Investigator as well as the study team must 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 an 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) should be used as a means of pseudo-anoymising parameters. This information should 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 (from a master randomization list [if applicable])

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 Chief 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.

9.2 Study documents

- A signed protocol and any subsequent amendments
- Current Summary of Product Characteristics/ Investigator's Brochure
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics/MHRA submissions/approvals/correspondence
- CVs of CI and site staff
- UK regulations (GCP) course certificate of each of trial team
- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study
- Sample IMP labels
- IMP accountability logs
- Delegation log

- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

9.3 Case report form

The case report form will be attached as a separate document.

9.4 Record retention and archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For trials involving BLT Trust patients, undertaken by Trust staff, or sponsored by BLT or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

9.4 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, Trust and Research Office policies and procedures and any subsequent amendments.

9.6 Clinical Governance Issues

9.6.1 Ethical considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

9.7 Quality control and quality assurance

9.7.1 Summary monitoring plan

The study is part of NIHR-HTA portfolio and will be monitored by the NIHR-HTA programme.

9.7.1 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

9.8 Serious breaches in GCP or the trial protocol

The sponsor of the Clinical Trial is responsible for notifying the licensing authority 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 (JRO) **within 24 hours**. The sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

9.9 Non-compliance

(A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP and UK regulations, which leads to prolonged collection of deviations, breaches or suspected fraud.)

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances 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. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the JRO will agree an appropriate action, including an on-site audit.

10. Trial Committees

10.1 Trial Steering Committee (TSC)

Trial Steering Committee (TSC) – will provide independent advice and support to the trial and report to the funder on trial progress. The TSC will be chaired by Dr Kristin Ullrich, an independent clinician with experience of pain trials plus two other independent members that will include patient and public involvement (PPI) and a health services research (HSR) methodologist plus the trial chief and principal investigators, trial manager and trial statistician. Given this is a feasibility study, the TSC will be asked to decide on the need for an separate independent Data Monitoring Committee (DMC) or whether DMC responsibilities can be subsumed within the roles of the TSC.

10.2 Trial Management Committee

Trial Management Group (TMG) – responsible for the overall management of the project. The TMG will comprise of all co-applicants, members of the study research team, local general practitioners

with a special interest in pain, and will have patient and public representation. Given the dispersed nature of the three clinical sites, meetings will primarily be by 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.

11. 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.

12. References

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The following is a list of attachments, those with an asterisk* must be submitted to the Research Ethics Committee with the protocol.

- Consent Form (versioned and dated appropriately)*
- Patient Information Sheet (versioned and dated appropriately)*
- GP letters/ advertisements/any other letters and documents to be given to the patient (versioned and dated appropriately)*
- An SAE/SUSAR reporting Organogram – who will be the study members (including BACK UP STAFF for ALL individuals) involved in the identification/reporting of the SAE
- Communication Plan Organogram – how will information be disseminated between the PI/CI and the members of the study team relating to the protocol and other trial related duties. This plan should ensure that there is always a physician (either PI/Sub-I) trained adequately on the study to ensure that a study trained medical physician is available to make any trial related decisions with regards to patient care, mainly with regards to adverse events or intercurrent illnesses.
- Source Data Identification List
- Core Lab Instructions To Investigators (if applicable)
- Specimen Preparation And Handling (if applicable) (e.g. for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for postage/courier/shipment)
- Drug Conversion Plan (if applicable) (e.g. if there is a special regimen for transitioning a subject from their baseline medication over to study medication)
- Antidote Preparation and Delivery (if applicable) (e.g. special instructions for preparing and delivering any therapy designed to reverse the effects of the study drug, if applicable)

The CRF should capture all of the revelant above elements/ data points (blood and non-blood). The CRF will capture all the revelant information to ensure that all the documented statistical information thus dictated in the protocol is captured and documented. This also serves to monitor at the sponsor level patient eligibility and safety.