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Abstract

Facet-joint injections for non-specific low back pain: a feasibility RCT

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Background: Pain of lumbar facet-joint origin is a common cause of low back pain in adults and may lead to chronic pain and disability, with associated health and socioeconomic implications. The socioeconomic burden includes an inability to return to work resulting in loss of productivity in addition to direct and indirect health-care utilisation costs. 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. 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. This pain may be treated by intra-articular injections with local anaesthetic and steroid, although this treatment is not standardised. At present, there is no definitive research to support the use of targeted lumbar facet-joint injections to manage this pain. Because of the lack of high-quality, robust clinical evidence, the National Institute for Health and Care Excellence (NICE) guidelines on the management of chronic low back pain [NICE. *Low Back Pain in Adults: Early Management*. Clinical guideline (CG88). London: NICE; 2009] did not recommend the use of spinal injections despite their perceived potential to reduce pain intensity and improve rehabilitation, with NICE calling for further research to be undertaken. The updated guidelines [NICE. *Low Back Pain and Sciatica in Over 16s: Assessment and Management*. NICE guideline (NG59). London: NICE; 2016] again do not recommend the use of spinal injections.

Objectives: To assess the feasibility of carrying out a definitive study to evaluate the clinical effectiveness and cost-effectiveness of lumbar facet-joint injections compared with a sham procedure in patients with non-specific low back pain of > 3 months' duration.

Design: Blinded parallel two-arm pilot randomised controlled trial.

Setting: Initially planned as a multicentre study involving three NHS trusts in the UK, recruitment took place in the pain and spinal orthopaedic clinics at Barts Health NHS Trust only.

Participants: Adult patients referred by their GP to the specialist clinics with non-specific low back pain of at least 3 months' duration despite NICE-recommended best non-invasive care (education and one of a

physical exercise programme, acupuncture or manual therapy). Patients who had already received lumbar facet-joint injections or who had had previous back surgery were excluded.

Interventions: Participants who had a positive result following a diagnostic test (single medial branch nerve blocks) were randomised and blinded to receive either intra-articular lumbar facet-joint injections with steroids (intervention group) or a sham procedure (control group). All participants were invited to attend a group-based combined physical and psychological (CPP) programme.

Main outcome measures: In addition to the primary outcome of feasibility, questionnaires were used to assess a range of pain-related (including the Brief Pain Inventory and Short-Form McGill Pain Questionnaire version 2) and disability-related (including the EuroQol-5 Dimensions five-level version and Oswestry Low Back Pain Questionnaire) issues. Health-care utilisation and cost data were also assessed. The questionnaire visits took place at baseline and at 6 weeks, 3 months and 6 months post randomisation. The outcome assessors were blinded to the allocation groups.

Results: Of 628 participants screened for eligibility, nine were randomised to receive the study intervention (intervention group, $n = 5$; sham group, $n = 4$), six completed the CPP programme and eight completed the study.

Limitations: Failure to achieve our expected recruitment targets led to early closure of the study by the funder.

Conclusions: Because of the small number of participants recruited to the study, we were unable to draw any conclusions about the clinical effectiveness or cost-effectiveness of intra-articular lumbar facet-joint injections in the management of non-specific low back pain. Although we did not achieve the target recruitment rate from the pain clinics, we demonstrated our ability to develop a robust study protocol and deliver the intended interventions safely to all nine randomised participants, thus addressing many of the feasibility objectives.

Future work: Stronger collaborations with primary care may improve the recruitment of patients earlier in their pain trajectory who are suitable for inclusion in a future trial.

Trial registration: EudraCT 2014-003187-20 and Current Controlled Trials ISRCTN12191542.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 21, No. 74. See the NIHR Journals Library website for further project information.

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Glossary

Best usual care As described in National Institute for Health and Care Excellence clinical guideline 88, *Low Back Pain: Early Management of Persistent Non-specific Low Back Pain*, best usual care includes 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.

Combined physical and psychological programme A group-based programme focused around education and targeted training of self-management skills, utilising a psychological approach to improve physical activity and functioning.

Definitive study An adequately powered randomised controlled trial to provide unequivocal evidence that supports or rejects the test hypothesis, for example whether or not a treatment shows a benefit to patients.

Feasibility study A study that asks whether or not something can be done, whether or not we should proceed with it and, if so, how.

Lumbar facet-joint injections The active intervention in which a needle is inserted into the facet-joint and a therapeutic substance, such as a steroid, is injected.

Sham procedure A dummy procedure in which a needle is inserted near the facet-joint but no therapeutic substance is injected.

List of abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
BeST	Back Skills Training
BPI	Brief Pain Inventory
CG	clinical guideline
CI	confidence interval
CPP	combined physical and psychological (programme)
DIRUM	Database of Instruments for Resource Use Measurement
DMC	Data Monitoring Committee
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions five-level version
FACET	Feasibility of Assessing the Clinical- and cost-Effectiveness of Therapeutic lumbar facet-joint injections
FJI	facet-joint injection
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
HTA	Health Technology Assessment
IMP	investigational medicinal product
JRMO	Joint Research Management Office
LBP	low back pain
MHRA	Medicines and Healthcare products Regulatory Agency
NG	NICE guideline
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	numerical rating scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSEQ	Pain Self-Efficacy Questionnaire
QALY	quality-adjusted life-year
SD	standard deviation
SF-12	Short Form questionnaire-12 items
SF-6D	Short Form questionnaire-6 Dimensions
SF-MPQ-2	short-form McGill Pain Questionnaire version 2
SPS	Stanford Presenteeism Scale
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale

Plain English summary

Lumbar facet-joints are small, paired joints in the lower back that provide stability, integrity and flexibility of movement of the spine. Diseased facet-joints may cause persistent low back pain. The current treatment options available in the UK include so-called lumbar facet-joint injections, when a needle is inserted into the joint and a therapeutic substance is injected. However, there is insufficient high-quality evidence to support their use and for this reason they were not approved in the latest national guidelines on the management of persistent low back pain.

This study aimed to see whether a large-scale study to assess lumbar facet-joint injections with steroid compared with a dummy or 'sham' procedure (a needle is inserted near the facet-joint but no therapeutic substance is injected) was possible.

We recruited patients with persistent low back pain from the pain clinics at Barts Health NHS Trust; those suitable to take part were randomly allocated to receive either lumbar facet-joint injections or a sham procedure. All participants were also invited to attend a combined physical and psychological programme consisting of six sessions of a psychologically informed group-based intervention of education and training, each lasting for 90 minutes, recommended as a strategy to reduce pain and its impact on a person's day-to-day life. Participants completed questionnaires about their pain and disability up until 6 months after their injections. Eight participants (the target estimate was 48 participants) completed the study before it was terminated by the funder.

We were unable to recruit the anticipated number of patients to the study as those attending the hospital pain clinics were not suitable for reasons such as they had received previous facet-joint injections or they were experiencing severe pain elsewhere other than the back. We therefore could not tell whether or not facet-joint injections are able to reduce low back pain or whether or not they are cost-effective. We were otherwise able to deliver the study as planned and without any significant problems.

We believe that it may be feasible to progress to a large-scale trial comparing facet-joint injections against a sham procedure by recruiting patients from other sources such as general practitioner surgeries.

Scientific summary

Background

The Global Burden of Disease Study (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**:1545–1602) has concluded that low back pain (LBP) causes more disability in the world than any other condition. LBP has a high lifetime prevalence, with significant economic and societal costs.

Common contributors to LBP in adults are thought to include lumbar facet-joints; treatment options for LBP with a likely facet-joint component include intra-articular facet-joint injections (FJIs), medial branch nerve blocks (which innervate the joints) or radiofrequency denervation of the medial branch nerves. Although the technique of lumbar FJI is not standardised, this typically involves injection of an active substance such as a corticosteroid into the joint.

The National Institute for Health and Care Excellence (NICE) guidelines for managing LBP were recently updated [NICE. *Low Back Pain and Sciatica in Over 16s: Assessment and Management*. NICE guideline (NG59). London: NICE; 2016] and do not recommend intra-articular FJIs on the grounds of there being insufficient high-quality evidence to support their use, recommending instead targeting the nerve supply of the facet-joints as the predominant pain generator source. Despite these recommendations, intra-articular FJIs remain in common use.

Review of the literature: a review of systematic reviews and meta-analyses

We undertook a literature search to identify systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar FJIs for chronic LBP. Eleven systematic reviews met the inclusion criteria and their methodological quality was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. Although 14 randomised controlled trials were identified across these reviews, no one review included all of these trials. The authors of these systematic reviews concluded that the level of clinical heterogeneity across included randomised controlled trials precluded any meta-analyses.

The conclusions drawn from the systematic reviews were generally equivocal. The limited to moderate quality of evidence to support the effectiveness of therapeutic lumbar FJIs in the management of chronic LBP indicates a need for further high-quality research in this area.

Rationale for a feasibility study

Because of the lack of high-quality, robust clinical evidence, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme issued a commissioning brief in 2011 to answer the research question, 'Is a definitive study to assess the effectiveness and cost-effectiveness of facet-joint injections compared with best non-invasive care for people with persistent non-specific low back pain feasible?'.

Objectives

We aimed to assess the feasibility of conducting a definitive study to evaluate the clinical effectiveness and cost-effectiveness of FJIs compared with a sham procedure in patients with non-specific LBP of > 3 months' duration. Specific objectives were to:

- assess the eligibility criteria and recruitment and retention of patients in the two treatment arms (FJIs vs. sham procedure) by assessing the feasibility of recruitment to inform a potential definitive study

- assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams
- assess the feasibility of the proposed definitive study design including testing of the randomisation and blinding procedures, development of an appropriate active and sham procedure for FJIs and assessment of the consistency of the trial sites in terms of delivering the combined physical and psychological (CPP) programme and their ability to collect the outcomes proposed for the main trial
- estimate outcome standard deviations (SDs) to inform the power calculation for a definitive study
- finalise the protocol design, statistical plan, number of centres required and study duration for the definitive study.

Methods

Study design

This feasibility study utilised a blinded parallel two-arm pilot randomised controlled trial design. A multicentre design was planned, with patients recruited from pain clinics at three participating NHS centres and their associated community-based pain clinics; however, recruitment took place at a single centre, Barts Health NHS Trust.

Participants

The study sought patients referred by their general practitioner (GP) to the pain and spinal orthopaedic clinics who had non-specific LBP of at least 3 months' duration and clinical indicators for pain of facet-joint origin, despite receiving at least two components of NICE-recommended best non-invasive care, including education and one of a physical exercise programme, acupuncture or manual therapy. Patients who had already received lumbar FJIs or who had had previous spinal surgery were excluded.

Following a positive diagnostic medial branch nerve block with lidocaine (> 50% pain relief on a numerical rating scale lasting for > 30 minutes), eligible participants were individually randomised in a 1 : 1 ratio to receive either the FJI (intervention group) or a sham (placebo injection) procedure (control group). The intervention group received intra-articular lumbar FJIs with local anaesthetic and steroid, whereas the sham group received periarticular injections with normal saline.

Both the intervention group and the control group received a CPP programme after their active or sham injections. At the time of establishing this study, NICE clinical guideline CG88 (2009) had recommended a CPP programme as part of best usual care.

Sample size calculation

At the outset of the study it was expected that a total of 60 patients would be recruited, to be able to estimate the precision of an assumed 20% attrition rate with an error of ±5% at the 95% confidence level. Assuming that 24 full data sets per arm were completed at the end of the study, this would give a reasonable estimate of the variance of outcomes.

Outcomes

The outcome questionnaire visits took place in research nurse-led clinics at baseline (pre randomisation) and at 6 weeks, 3 months and 6 months post randomisation. The outcome questionnaires covered a range of pain- and disability-related issues including pain intensity and characteristics, use of co-analgesics in the previous week, lack of efficacy or side effects of pain relief, expectation of benefit, health-related quality of life, functional impairment, satisfaction with treatment, complications and adverse events, co-psychological well-being, health-care utilisation and costs and impact on productivity.

Statistical analysis

As this was a feasibility study, it was not planned to formally inferentially test differences in outcomes or costs between or within the groups. Mean recruitment and attrition rates were calculated with 95% confidence intervals. Means and SDs for all outcomes for the two groups at baseline and at all follow-up visits were reported. A detailed statistical analysis plan was prepared by the study statistician prior to any data analysis. Analyses were performed blinded to group allocation.

Health economics analysis

A health economics analysis plan was developed in collaboration with the study's health economist and statistician. A formal economic analysis was not proposed (as this was a feasibility study). Any outcomes from this feasibility study would be used in the design of the definitive study. In particular, the analysis looked at the ability to collect the outcomes proposed for the main trial.

Results

Although recruitment was planned across three centres, given the delays in study set-up the funder directed that this take place at only one centre, Barts Health NHS Trust. Recruitment took place over 9 months, with the first participant recruited in January 2016 and the last participant recruited in September 2016.

During the recruitment period, 628 patients referred to the recruiting clinics by their GP with non-specific LBP were screened for eligibility to enter the study. Of the 50 patients who met the inclusion criteria, 16 agreed to take part in the study and 11 received the diagnostic test for facet-joint disease. Nine participants had a positive response and were randomised to receive either lumbar FJIs with steroid or a sham procedure. Eight participants completed the study; one randomised participant was lost to follow-up.

The participant screening-to-recruitment ratio was 70 : 1 (628 : 9), which contrasts with an expected prestudy ratio of 17 : 1 (1000 : 60). The recruitment rate varied between zero and four patients per month. The main reasons for screening failure included that patients had received previous lumbar FJIs ($n = 192$), had other dominant or widespread pain ($n = 92$) or had radicular pain ($n = 64$).

Each pain consultant visit was associated with a cost of £148.03 and the delivery of the intervention or sham procedure incurred a cost of £691 per patient. The CPP programme had a mean cost of £2500 per patient. The intervention group was observed to have higher resource use costs than the sham group, with a cost of £193 (SD £219) per participant in the intervention group and a cost of £75 (SD £73) per participant in the sham group. Although there are limitations of the analysis associated with the highly skewed costs and small sample size, this suggests that a potential downstream effect of FJI is a subsequent increase in medication use and associated costs within primary care.

Discussion

The small number of participants recruited to the study and the feasibility design preclude us from drawing any conclusions on the clinical effectiveness or cost-effectiveness of intra-articular lumbar FJIs in the management of non-specific LBP. However, the clinical procedures used appeared to be safe and well tolerated, with no significant adverse events related to the steroid injection. Furthermore, we were able to successfully collect clinical and economic outcomes from the majority of patients over the duration of the study.

Cost differences were identified between the intervention group and the sham group in the feasibility study, which may be a reflection of the inherent skewness in the data and the very small sample size.

The main weakness of the study was the failure to achieve our expected recruitment target and the consequent early closure of the study by the funder. There were substantial system-level barriers that the study team were unable to control, which led to long delays in obtaining research governance.

It became clear early in the recruitment phase that many patients presenting to the pain clinics with LBP of > 3 months' duration were not suitable for the study and that patients screened in the spinal orthopaedic clinics also did not meet the eligibility criteria. Despite employing additional strategies in the final stages of recruitment, we conclude that patients presenting to these hospital-based specialist clinics were generally not suitable because of the complexity of their pain problems and that we may have had better success in recruiting from primary care-based services.

We were unable to meet our feasibility objective of a recruitment target of 60 randomised LBP patients across three investigative sites. Instead, we were able to randomise only nine patients at one investigative site. However, we believe that we met our other pre-stated feasibility objectives, as detailed in the following sections.

Assess the eligibility criteria and recruitment and retention of patients in the two treatment arms

Recruitment took place at a single centre only, largely because of delays in study set-up and a decision by the funder to terminate the study early because of the lack of time available to open the other two sites. A number of reasons for the delays have been identified, including regulatory issues, staffing problems, specific recruitment challenges, factors affecting clinician and patient participation and the study population itself.

Assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams

A Delphi exercise was undertaken by 42 interventional pain physicians in the UK to agree on the methods for the FJI and sham procedures; the two treatment arms can therefore be considered to be feasible and acceptable by pain clinicians.

Of the 34 patients who met the eligibility criteria but who declined to take part in the study, none cited the lack of acceptability of the two treatment arms as the reason for not wishing to take part.

Assess the feasibility of the proposed definitive study design

We believe that this feasibility study did allow us to demonstrate the feasibility of the study design to inform a definitive study. We were able to develop an appropriate active injection technique and sham procedure. No patients refused participation on the grounds of randomisation to an active or a sham procedure. We were able to maintain the blinding of patients and clinicians. The CPP programme was consistently delivered to small groups of participants and was well aligned to the latest NICE guidelines (NICE, 2106).

Estimate outcome standard deviations to inform the power calculation for a definitive study

We reported the SDs for all proposed clinical and economic outcomes at baseline and follow-up but would express caution in using these SDs to inform the sample calculation for a future definitive study because of the small sample size. Probably the only parameter for a future definitive study that this study was able to estimate with precision was the screening/recruitment rate.

Finalise the protocol design, statistical plan, number of centres required and study duration of the definitive study

Given the failure to meet the study recruitment target and the small number of patients recruited from one centre, the study team deemed it inappropriate to present a finalised protocol for a definitive study on the basis of this feasibility study.

Conclusions

A successful trial can be defined as one that achieves success in recruitment and is able to answer the research questions. Although we have successfully demonstrated our ability to develop a robust study protocol and deliver the intended interventions, and address many of the feasibility objectives, failure to achieve the target recruitment rate remains a key finding of this study. However, there are lessons learned here that can be used to inform and improve patient recruitment for a future definitive study.

Two research teams were funded by the NIHR to answer the research questions: (1) the Facet Feasibility study (the addition of intra-articular FJIs to best usual non-invasive care) (reference number HTA 11/31/01) led by Professor Martin Underwood, University of Warwick, and (2) this project, the FACET (Feasibility of Assessing the Clinical- and cost-Effectiveness of Therapeutic lumbar facet-joint injections) feasibility study, led by Professor Richard Langford, Barts Health NHS Trust. Neither research team met the target recruitment rate and Professor Underwood's team concluded that a definitive study is indeed feasible but that recruitment from pain clinics alone was insufficient. Both teams experienced significant delays in study set-up.

Based on our findings, we would agree with the Underwood team that a definitive study is potentially feasible, with adjustments made to the target population and increased primary care involvement to enable patients to be screened earlier in their pain trajectory. To optimise recruitment for a definitive study, we would contend that any future studies in this area should involve stronger collaborations with primary care physicians and musculoskeletal physiotherapists with the aim of making these procedures more accessible to these patients who would not otherwise have been referred on for specialist services.

Trial registration

This trial is registered as EudraCT 2014-003187-20 and Current Controlled Trials ISRCTN12191542.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Funding history

The FACET (Feasibility of Assessing the Clinical- and cost-Effectiveness of Therapeutic lumbar facet-joint injections) feasibility study was a commissioned proposal funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (reference number HTA 11/31/02); the funding contract was agreed in July 2013. A favourable ethical opinion was given on 21 May 2015 and NHS permission was granted on 20 January 2016, with the first participant recruited to the study on 22 January 2016. Following an extension agreement with the funder, recruitment ended on 30 September 2016 and the study closed on 31 March 2017.

Structure of this report

In this chapter, the existing evidence for therapeutic intra-articular lumbar facet-joint injections (FJIs) for non-specific low back pain (LBP) is reviewed and the need for a pilot trial is presented. In *Chapter 2* the feasibility study procedure and associated methodological work are described, with the results of this work being presented in *Chapter 3*. The implications of our findings are discussed in *Chapter 4* and the conclusions drawn with regard to a full trial are presented in *Chapter 5*.

Background

Low back pain causes more global disability than any other condition, and has a lifetime prevalence of up to 85%.[1] Non-specific LBP, in which symptoms are experienced without any recognisable pathology,[2] is thought to affect around 90% of all LBP sufferers, with between 1% and 5% of patients presenting with LBP having a serious spinal pathology such as vertebral fracture, malignancy, infection and inflammatory disease.[3]

The economic costs of LBP have been reported to be £12.3B per annum in the UK alone.[4] Chronic LBP, with a prevalence of 3–10%,[5] is associated with depression, anxiety, deactivation, inability to work and substantial societal costs.[1,6]

Common contributors to LBP in adults are thought to include lumbar facet-joints.[7] These 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 contributions to LBP may arise from any structure that is part of the facet-joints, including the fibrous capsule, synovial membrane, hyaline cartilage and bone.

Low back pain with a likely facet-joint component can be treated with interventions targeting the facet-joints, including intra-articular (within the joint itself) FJIs, periarticular medial branch nerve blocks or radiofrequency denervation of the medial branch nerves innervating the joints. The technique of FJI is not standardised and may be carried out with or without radiological guidance to confirm needle placement.[8] Lumbar FJIs involve the injection of an active substance, typically steroids with or without a local anaesthetic, intra-articularly or next to the joint (periarticular injections). They are commonly carried out under radiological or fluoroscopic guidance, although they can be performed under ultrasound or computerised tomography scanning guidance.[9]

The National Institute for Health and Care Excellence (NICE) guidelines for managing LBP were recently updated [NICE guideline (NG59)[10]]. These guidelines propose a care pathway in which all those aged ≥ 16 years with LBP with or without sciatica should be provided with advice and information, tailored to their needs and capabilities, to help them self-manage at all steps of the treatment pathway, including education on the nature of LBP and sciatica and encouragement to return to work and pursue normal activities of daily living.[11] Those with a specific episode or flare-up of LBP should consider a group exercise programme, manual treatment or a psychological therapy package. If these therapies fail, pharmacological options and combined physical and psychological (CPP) programmes should be offered, followed by radiofrequency denervation or surgical approaches such as fusion. The guidelines make specific 'do not use' recommendations for a range of groups of treatments including acupuncture and electrotherapy; traction, braces and corsets; disc replacement; and spinal injections (including FJIs). The NICE guidelines omit intra-articular FJIs on the grounds of there being insufficient high-quality evidence to support their use and recommend instead targeting the facet-joints' nerve supply (medial branch nerves) as the predominant pain generator source. However, intra-articular FJIs remain in common use.[12]

Review of the literature: a review of systematic reviews and meta-analyses

We undertook a literature search to identify systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar FJIs for chronic LBP. We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials from 1966 to February 2017; the search strategies used are detailed in *Appendix 1*. Two reviewers (Saowarat Snidvongs and Fausto Morell-Ducos) independently screened and assessed full-text articles for eligibility. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is illustrated in *Figure 1*. Eleven systematic reviews[14–24] met the inclusion criteria; the sources of the reviews are summarised in *Appendix 2*. The Assessment of Multiple Systematic Reviews (AMSTAR) checklist,[25] applied by two independent reviewers to assess the methodological quality of the systematic reviews, demonstrated significant variations between the reviews, with AMSTAR scores ranging between 2 and 10 out of a maximum of 11 points, as shown in *Appendix 3* (a low score is associated with a higher risk of bias).

In total, 14 randomised controlled trials were identified across these 11 reviews; 13 were obtained as full-text articles and their findings are summarised in *Table 1*. *Appendix 4* illustrates that, given the variation in dates when the reviews were undertaken and their precise inclusion/exclusion criteria, no one review included all of these trials. The authors of these systematic reviews concluded that the level of clinical heterogeneity across the included randomised controlled trials – different injection procedures, substances and comparators – precluded any meta-analyses.

The conclusions drawn from the systematic reviews were generally equivocal. Although there was some trial evidence demonstrating the effectiveness of therapeutic lumbar FJIs in the management of chronic LBP, the limited to moderate quality of this evidence was insufficient to support their use in practice. The current evidence base for FJI is neatly summed up by a recent and high-quality systematic review by Vekaria *et al.*,[23] which concluded that 'The studies found here were clinically diverse and precluded any meta-analysis. A number of methodological issues were identified. The positive results, whilst interpreted with caution, do suggest that there is a need for further high-quality work in this area.'[23]

Rationale for a feasibility study

To provide further high-quality research in this area, the NIHR HTA programme issued a commissioning brief in 2011 to answer the research question, 'Is a definitive study to assess the effectiveness and cost-effectiveness of facet-joint injections compared with best non-invasive care for people with persistent non-specific low back pain feasible?' [see www.journalslibrary.nihr.ac.uk/programmes/hta/113102/#/ (accessed 31 October 2017)].

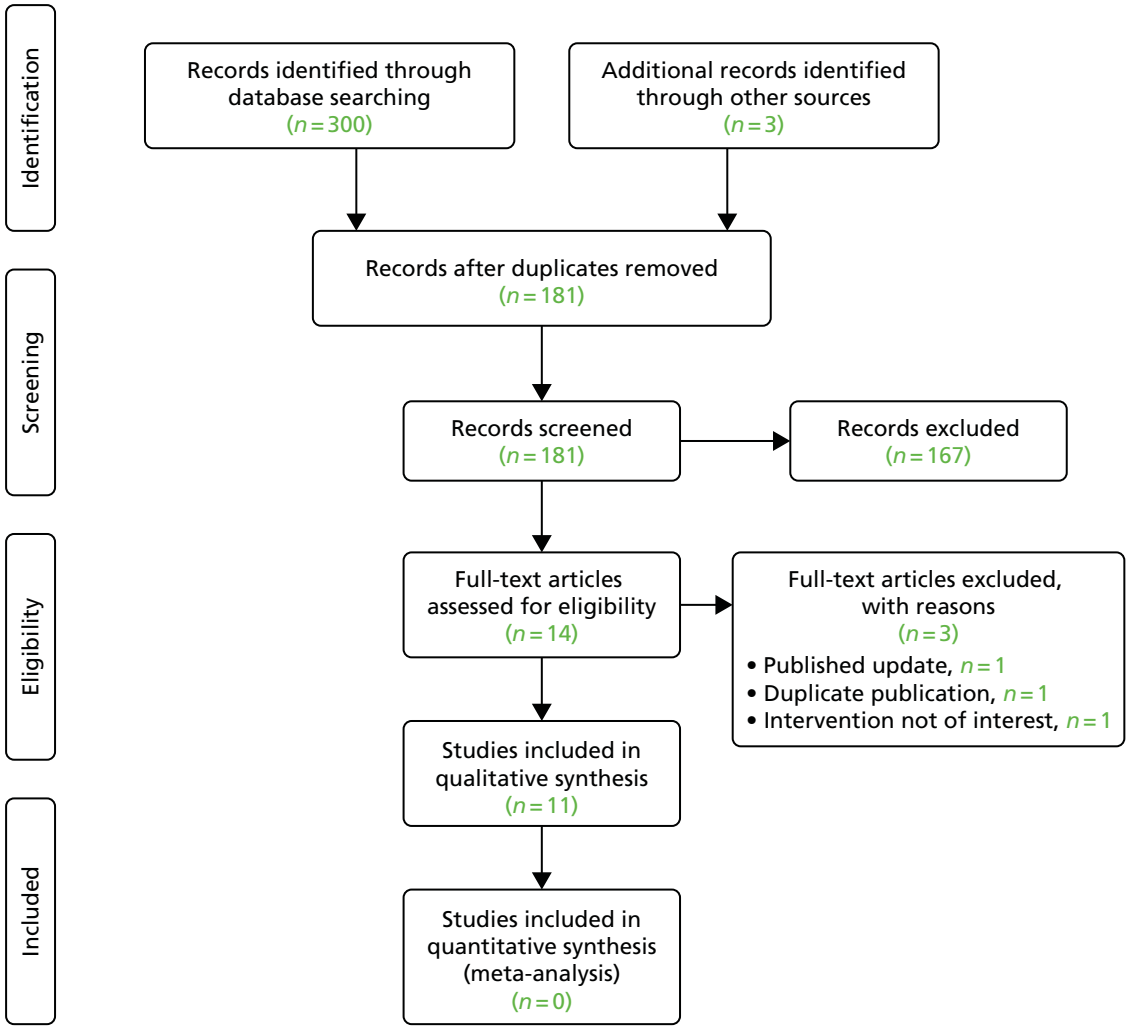

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the systematic review search. Adapted from Moher *et al.*[13] © 2009 Moher *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Two research teams were funded by the NIHR in response to this commissioned call: (1) the Facet Feasibility study (the addition of intra-articular facet-joint injections to best usual non-invasive care) (reference HTA 11/31/01) led by Professor Martin Underwood, University of Warwick [see www.journalslibrary.nihr.ac.uk/programmes/hta/113101/#/ (accessed 31 October 2017)] and (2) this project, the FACET feasibility study (a multicentre double-blind randomised controlled trial comparing intra-articular lumbar facet-joint injections with a sham procedure, followed by a combined physical and psychological programme) (reference HTA 11/31/02) [see www.journalslibrary.nihr.ac.uk/programmes/hta/113102/#/ (accessed 31 October 2017)] led by Professor Richard Langford, Barts Health NHS Trust.

Study aims and research questions

The aim of the FACET feasibility study was to assess the feasibility of conducting a definitive study to evaluate the clinical effectiveness and cost-effectiveness of FJIs compared with a sham procedure in patients with non-specific LBP of > 3 months' duration.

TABLE 1 Randomised controlled trials of the efficacy of therapeutic FJIs identified in previous systematic reviews

First author, year (country, *n* randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up (months)	Key findings
Lilius, 1989[26] (Finland, *n* = 109)	Unilateral LBP for > 3 months, failed analgesics and physiotherapy, no diagnostic blocks	(1) Radiologically guided intra-articular lumbar FJIs with bupivacaine and methylprednisolone; (2) radiologically guided pericapsular injections with bupivacaine and methylprednisolone	Sham (radiologically guided intra-articular lumbar FJIs with physiological saline)	Not stated – assessed pain, disability and return to work	3 months	No difference in outcomes at follow-up between the two active groups and the sham group. Improvement in pain, disability and work attendance in all groups
Carette, 1991[27] (Canada, *n* = 101)	LBP for > 6 months, normal neurological examination, > 50% pain reduction after single intra-articular diagnostic injection with lidocaine	Fluoroscopy-guided intra-articular lumbar FJIs with methylprednisolone and isotonic saline	Sham (fluoroscopy-guided intra-articular lumbar FJIs with isotonic saline)	Not stated – assessed pain severity, back mobility and limitation of function	6 months	No differences in outcomes at 1 and 3 months between the two groups. At 6 months, patients in the intervention group reported greater self-rated improvement, lower pain intensity and less physical disability than patients in the sham group
Marks, 1992[28] (Scotland, UK, *n* = 86)	LBP for > 6 months, failed non-narcotic analgesics and physiotherapy, no diagnostic blocks	Radiologically guided intra-articular lumbar FJIs with lidocaine and methylprednisolone	Radiologically guided lumbar facet-joint medial branch nerve blocks with lidocaine and methylprednisolone	Pain intensity	3 months	Marginally longer duration of response in the intervention group after 1 month, otherwise no difference in outcomes at other time points between the two groups. Some short-term pain relief seen in both groups
Revel, 1998[29] (France, *n* = 80)	LBP for > 3 months, failed analgesics and physical therapy, no diagnostic blocks	Fluoroscopy-guided intra-articular lumbar FJIs with lidocaine plus periarticular corticosteroid steroid injection (not evaluated)	Fluoroscopy-guided intra-articular lumbar FJIs with saline plus periarticular corticosteroid steroid injection (not evaluated)	Pain intensity using VAS	30 minutes after injections	Significantly reduced pain scores in the intervention group compared with the comparator group

First author, year (country, *n* randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up (months)	Key findings
Manchikanti, 2001[30] (USA, *n* = 84)	LBP for > 6 months, failed conservative management, positive response following controlled comparative diagnostic blocks with lidocaine and bupivacaine	Lumbar facet medial branch nerve blocks with lidocaine or bupivacaine, Sarapin® (High Chemical Company, Levittown, PA, USA) and methylprednisolone	Lumbar facet medial branch nerve blocks with lidocaine or bupivacaine and Sarapin	Not stated – assessed pain characteristics, physical health, mental health, functional status, return to work and narcotic intake	Up to 2.5 years	No difference in outcomes at follow-up between the groups; improvement in pain and functional outcomes in groups I (IA and IB) and II (IIA and IIB)
Mayer, 2004[31] (USA, *n* = 70)	'Chronic disabling work related lumbar spinal disorder' for > 6–12 months, 'lumbar segmental rigidity' on clinical examination, no diagnostic blocks	Fluoroscopy-guided bilateral intra-articular lumbar FJIs with lidocaine, bupivacaine and depot corticosteroid and home stretching exercise programme	Home stretching exercise programme only	Range of motion, pain and disability	Not specified – after completing the home stretching exercise programme	No difference in pain and disability reported at follow-up between the two groups, but greater improvement in range of motion in the intervention group
Fuchs, 2005[32] (Germany, *n* = 60)	LBP for > 3 months, facet-joint osteoarthritis on imaging	Computerised tomography-guided intra-articular lumbar FJIs with triamcinolone	Computerised tomography-guided intra-articular FJIs with sodium hyaluronate	Pain intensity, functioning and quality of life	180 days	No difference in outcomes at follow-up between the two active groups; improvement in pain and functional outcomes in both groups
Manchikanti, 2008[33] (USA, *n* = 120)	LBP for > 6 months, failed conservative management, 80% pain relief following controlled comparative diagnostic blocks with lidocaine and bupivacaine	IA: lumbar facet-joint medial branch nerve blocks with bupivacaine; IB: lumbar facet-joint medial branch nerve blocks with bupivacaine and Sarapin	IIA: lumbar facet-joint medial branch nerve blocks with bupivacaine and steroid; and IIB: lumbar facet-joint medial branch nerve blocks with bupivacaine, steroid and Sarapin	Not stated – assessed pain relief, work status, opioid intake and functional status	1 year	No difference in outcomes at follow-up between the groups; improvement in pain and functional outcomes in both groups
Kawu, 2011[34] (Nigeria, *n* = 18)	LBP for > 3 months, failed analgesics, MRI features of facet-joint arthropathy, no diagnostic blocks	Radiologically guided lumbar FJIs with bupivacaine and methylprednisolone	Physiotherapy (McKenzie regimen)	Not stated – assessed pain relief and satisfaction with treatment	6 months	Greater decreases in pain and higher levels of satisfaction in the intervention group than in the comparator group

continued

TABLE 1 Randomised controlled trials of the efficacy of therapeutic FJIs identified in previous systematic reviews (*continued*)

First author, year (country, *n* randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up (months)	Key findings
Celik, 2011[35] (Turkey, $n = 80$)	LBP for < 4 months, no diagnostic blocks	Fluoroscopy-guided lumbar FJIs with bupivacaine and methylprednisolone	Diclofenac, thiocolchicoside and bed rest for 4 days	Not stated – assessed LBP disability and pain intensity	6 months	Greater decreases in pain and disability in the intervention group than in the comparator group; improvement in pain and functional outcomes in both groups
Yun, 2012[36] (Korea, $n = 57$)	LBP (no duration specified), clinical indicators of facet syndrome, no diagnostic blocks	Fluoroscopy-guided lumbar FJIs with lidocaine and triamcinolone	Ultrasound-guided lumbar FJIs with lidocaine and triamcinolone	Pain and activities of daily living	3 months	No difference in outcomes at follow-up between the two active groups; improvement in pain and functional outcomes in both groups
Ribeiro, 2013[37] (Brazil, $n = 60$)	LBP for > 3 months, clinical diagnosis of lumbar facet-joint syndrome, no diagnostic blocks	Fluoroscopy-guided intra-articular lumbar FJIs with lidocaine and triamcinolone	Intramuscular paravertebral injections with lidocaine and triamcinolone	Not stated – assessed quality of life, functional capacity, pain on back extension, percentage improvement scale, analgesic usage	24 weeks	'Slightly superior' results in the intervention group than in the comparator group; improvement in pain and functional outcomes in both groups
Lakemeier, 2013[38] (Germany, $n = 56$)	LBP for > 24 months, > 50% pain reduction after single intra-articular diagnostic injection with bupivacaine	Fluoroscopy-guided intra-articular lumbar FJIs with bupivacaine and betamethasone	Radiofrequency denervation of the lumbar facet-joint medial branch nerves	LBP-related disability using the Rowland Morris Disability Questionnaire	6 months	No difference in outcomes at follow-up between the two active groups; improvement in pain and functional outcomes in both groups

MRI, magnetic resonance imaging; VAS, visual analogue scale.

To inform a full trial, a number of questions first need to be assessed by a feasibility study:

1. Given the multiple sites with the 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 a sufficient number of patients be recruited and retained?

Study objectives

- To assess the eligibility criteria and recruitment and retention of patients in the two treatment arms (FJIs vs. sham procedure) by assessing the feasibility of recruitment in the three centres, reviewing the number of completed patient data sets, auditing the quality of data entry at the centres and assessing and analysing any protocol violations (such as failure to deliver the CPP programme – recommended therapy at the time of the establishing this study[39]), side effects and other adverse outcomes.
- To assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams.
- To assess the feasibility of the proposed definitive study design, including:
    - testing of the randomisation and blinding procedures
    - development of appropriate active and sham procedures for FJIs
    - assessment of the consistency of the trial sites in terms of delivering the CPP programme
    - assessment of the 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).
- To estimate outcome standard deviations (SDs) to inform the power calculation for a definitive study.
- To finalise the protocol design, statistical plan, number of centres required and study duration for the definitive study.

Chapter 2 Methods

Study design

This feasibility study utilised a blinded parallel two-arm pilot randomised controlled trial design. Following a positive diagnostic medial branch nerve block, participants with non-specific LBP were individually randomised in a 1 : 1 ratio to receive either the FJI (intervention group) or a sham (placebo injection) procedure (control group). Both the intervention group and the control group received a CPP programme after their active or sham injections.

Participants

The study sought patients with non-specific LBP based on the following inclusion and exclusion criteria.

Inclusion criteria

- Patients aged 18–70 years attending pain clinics identified during routine clinical assessment of non-specific LBP. Clinical indicators of pain of facet-joint origin included tenderness over the facet-joints, referred leg pain above the knees and worsening pain on extension, flexion and rotation of the lumbar spine.
- Low back pain of $\geq$ 3 months' duration.
- An average pain intensity score of $\geq$ 4 out of 10 in the 7 days preceding recruitment despite NICE-recommended treatment. NICE clinical guideline CG88[7] recommended providing patients with advice and information to promote self-management of their LBP 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.
- Dominantly paraspinal (not midline) tenderness at two bilateral lumbar levels.
- At least two components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture or manual therapy.[7]
- Patients are suitable for the FJIs.

Exclusion criteria

- Patient refusal to consent.
- More than four painful lumbar facet-joints. No more than four facet-joints were to be injected to limit the total dose of intra-articular steroids.
- 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 or manual therapy.[7]
- '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.[40]
- Known hypersensitivity to study medications.
- Dominantly midline tenderness over the lumbar spine, any other dominant pain or radicular pain.
- 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.
- Any active neoplastic disease, including primary or secondary neoplasm.
- Pregnant or breastfeeding patients (verbal confirmation obtained at screening; prior to each interventional procedure involving radiography, local hospital procedures will be followed to confirm that female participants are not pregnant).

- Any evidence of previous lumbar FJIs, previous lumbar spinal surgery or any major trauma or infection to the lumbar spine.
- Patients with morbid obesity (body mass index of $\geq$ 35 kg/m^2).
- Participation in another clinical trial of an investigational medicinal product or disease-related intervention in the past 30 days.
- Patients unable to commit to the 6-month study duration.
- Patients involved in legal actions or employment or benefit tribunals related to their LBP.
- Patients with a known history of substance abuse.

Recruitment procedures

It was originally planned to recruit patients from pain clinics at the three participating NHS centres and their associated community based pain clinics. However, because of the early termination of the study by the funder, recruitment was undertaken at only one centre, Barts Health NHS Trust. Recruitment took place over 9 months. The first participant was recruited in January 2016 and the last participant was recruited in September 2016.

Patients were referred by their general practitioner (GP) as a standard clinical referral with LBP requiring further specialist assessment, for reasons such as uncertain diagnosis, failure of conservative treatment and expectation of therapeutic interventions. Potentially eligible patients were identified by a pain clinician based on the inclusion and exclusion criteria.

Participants were free to withdraw from the study at any time without giving a reason; the participant information sheet stated that 'a decision to withdraw from the study at any time will not affect the standard of care that you receive now or in the future' (see *Appendix 5*). Participants who withdrew from the study received a routine follow-up appointment in their pain clinic for continuing assessment and management by their pain physician.

Informed consent

Potential participants were given a copy of the information sheet (see *Appendix 5*) and a verbal explanation of its contents, including information 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. A medically qualified investigator on the delegation log obtained written informed consent.

Sample size calculation

At the outset of the study it was expected that a total of 60 patients would be recruited, to be able to estimate the precision of an assumed 20% attrition rate with an error of $\pm$5% at the 95% confidence level. Assuming that 24 full data sets per arm were completed at the end of the study, this would give a reasonable estimate of variance of the outcomes.[41]

Diagnostic test

Following screening and consent, all participants underwent a diagnostic medial branch nerve block. Those who achieved a positive response were randomised to the intervention group or the control (sham) group.

The diagnostic medial branch nerve injections were carried out at each painful lumbar level under radiological guidance. With the patient lying in the prone position on a radiolucent table, the investigator

examined the patient's back to elicit paraspinal tenderness and confirmed appropriate landmarks and facet-joints to be injected using radiological image intensification. The C-arm of the image intensifier was obliquely rotated as required to facilitate visualisation of the target for injection. The spinal needle was used to inject 0.5 ml of 1% lidocaine per level, with six levels injected. A positive response was defined as a $\geq$ 50% pain reduction lasting for > 30 minutes, that is, the duration of action of lidocaine, measured using a pain intensity numerical rating scale (NRS) and assessed in the standing position.

Interventions

The FJIs, sham procedure and diagnostic tests were carried out by the Principal Investigator at Barts Health NHS Trust, a Fellow of the Faculty of Pain Medicine of the Royal College of Anaesthetists in the UK. During all of the interventional procedures strict aseptic conditions were adhered to and local theatre protocols were followed with regard to admission and discharge criteria, including the use of the World Health Organization (WHO) Surgical Safety Checklist[42] to identify the correct patient prior to starting the procedure. The investigator carrying out the injections was not blinded to randomisation group.

Active injection

Before undertaking this feasibility study, a web-based survey of 250 UK pain specialists was carried out utilising the Delphi method to agree on the choice of needle, injectate and volume of injection, as well as the choice of steroid, dose and volume and maximum dose of steroid (see *Appendix 6*).

In the intervention group, each participant received four FJIs at two bilateral lumbar levels, with 0.5 ml of 0.5% bupivacaine (Marcain Polyamp Steripack 0.5%, Aspen Pharma Trading Limited, Dublin, Ireland) and 20 mg of methylprednisolone (Depo-Medrone 40 mg/ml, Pfizer, Kent, UK) injected per joint. No more than four facet-joints were to be injected to avoid any potential confounding effect attributable to the systematic action of exceeding 80 mg of methylprednisolone. The volume of injectate did not exceed 1 ml per joint as it would be possible to rupture the intra-articular capsule with greater volumes, spreading the local anaesthetic and steroid to other potentially pain-generating structures.

Paraspinal tenderness was elicited as described previously. The skin was anaesthetised with 1% lidocaine (Lidocaine Hydrochloride Injection BP 1% w/v, Hameln Pharmaceuticals Ltd, Gloucester, UK) and a 22G 90-mm Quincke spinal needle was advanced through the skin, subcutaneous tissue and paraspinal muscle towards the facet-joint under radiological guidance. Entry of the needle was confirmed by visualisation of the needle position within the joint space and local anaesthetic and steroid were injected into the joint.

Sham procedure

The control group received four injections of 0.5 ml of normal saline (0.9% sodium chloride) at two bilateral lumbar levels. A low volume was chosen 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 would not receive systematic steroid administration as it has been shown that the addition of parenteral steroid does not contribute to the pain relief achieved by targeted injections.[43]

Paraspinal tenderness was elicited as described previously. The skin was anaesthetised with 1% lidocaine and a 22G 90-mm Quincke spinal needle was advanced through the skin, subcutaneous tissue and paraspinal muscle towards the periarticular space under radiological guidance. Placement of the needle in the periarticular space was confirmed by visualisation of the needle position next to the joint space and normal saline was injected at this site.

Combined physical and psychological programme

Both the intervention group and the control group underwent a CPP programme delivered by trained physiotherapists. Research on CPP management of LBP has demonstrated that equally effective management can be achieved with far fewer than the 100 hours prescribed in the 2009 NICE guidance.[7]

The study therefore proposed to deliver a programme drawing on the methods and evidence from the Back Skills Training (BeST) trial.[44]

Physiotherapists on the delegation log were trained to deliver the Back Skills Training programme by the lead physiotherapist. Individual physiotherapists undertook approximately 10 hours of online training at www.backskillstraining.co.uk (accessed 11 November 2017) and received a certificate of completion and a trainer manual to support CPP programme delivery. The lead physiotherapist organised face-to-face meetings with each physiotherapist to ensure competency and standardised delivery.

Each participant attended an initial one-to-one hour-long assessment with a trained physiotherapist at which information was gathered, including the impact of pain on their activity and their thoughts and beliefs regarding LBP. Individualised goals were identified with one specific to physical activity. Participants then selected and practised an individualised exercise programme.

Six weekly 1.5-hour sessions of a group-based CPP programme were scheduled for each participant. Completion of the CPP programme was defined as having completed a minimum of four out of six sessions. The session contents are detailed on the website www.backskillstraining.co.uk and address the following:

- understanding pain
- pain fluctuations
- unhelpful thoughts and feelings
- restarting activities or hobbies
- when pain worries us
- coping with flare-ups.

One session per programme was observed by the lead physiotherapist to assess consistency of delivery and to provide feedback and support for the physiotherapists running the course. Two research physiotherapists in total, including the lead physiotherapist, delivered the programme to the study participants at Barts Health NHS Trust.

Each participant received a Back Skills Training Patient Workbook, which provided a summary of each week's content for their reference at home. It was expected that participants would be in groups of fewer than 10 people; four to five groups of four to five participants per site were anticipated.

Regulatory approvals

The study was conducted in compliance with the principles of the Declaration of Helsinki (1996)[45] and the principles of Good Clinical Practice[46] and in accord with all applicable regulatory requirements including but not limited to the Research Governance Framework[47] and the Medicines for Human Use (Clinical Trials) Regulations 2004,[48] as amended in 2006 and 2008, the sponsor's policies and procedures and any subsequent amendments.

The required regulatory approvals were obtained in the UK. The study received ethics approval from the National Research Ethics Service (NRES) Committee London – City & East (reference 15/LO/0500) and clinical trial authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) (reference 14620/0046/001–0001). The trial protocol was reviewed by the MHRA's clinical trials team and the trial was considered to be a type A Clinical Trial of an Investigational Medicinal Product (CTIMP), that is, the risks are no higher than those of standard medical care. The Summary of Product Characteristics (SmPCs) for each investigational medical product (bupivacaine and methylprednisolone acetate) are available to view on the Electronic Medicines Compendium.[49,50] Health Research Authority (HRA) approval was obtained and the study was given permission by the sponsor's Joint Research Management Office (JRMO) to recruit patients at Barts Health NHS Trust.

Imaging authorisation was given by the sponsor's clinical radiation expert and medical physics expert, as all of the participants would receive ionising radiation in the form of X-rays for the diagnostic injections, FJIs and sham procedure.

Randomisation and blinding

Participants were allocated to either the intervention group or the control group in a 1 : 1 ratio, with stratification by centre and minimisation on baseline pain scores (categories). To ensure concealment, the allocation sequence was computer generated and provided through a password-protected web-based portal developed and maintained by the Peninsula Clinical Trials Unit (PenCTU).

It was not possible to blind the operator (Principal Investigator) as the injections were intentionally given at different sites (intra-articular vs. periarticular) and the injections looked different (methylprednisolone is provided as a cloudy suspension, whereas the sham injection was clear). However, study participants and the remainder of the research team, including the Chief Investigator, research nurses conducting the outcome assessments and data analysts, were blinded for the duration of the study. Unblinding took place at the end of the study once data analysis had been completed. A standard operating procedure was in place for emergency unblinding, in accordance with the sponsor guidelines.

Outcomes

The outcome questionnaire visits took place in research nurse-led clinics at baseline (pre randomisation) and at 6 weeks, 3 months and 6 months post randomisation. A sample case report form is shown in *Appendix 7* and the schedule of outcome assessment is shown in *Table 2*. The outcome questionnaire covered a range of pain- and disability-related issues and was in accord with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)-recommended core outcome measures for chronic pain trials.[51] The following assessment tools were used in the study.

- Pain intensity and characteristics – Brief Pain Inventory (BPI) (Short Form) Modified,[52] with its 11-point NRS, and short-form McGill Pain Questionnaire version 2 (SF-MPQ-2).[53] As movement could potentially influence the intervention (lumbar FJIs or sham procedure), all numerical rating scores were assessed in the standing position.
- Use of co-analgesics in the previous week – participant self-report.
- Lack of efficacy of pain relief, or, for side effects, early withdrawal from the study.
- Expectation of benefit (asked at baseline only) – measured on a scale from 0 to 6, ranging from 'expect no improvement' to 'expect total improvement'.
- Health-related quality of life – EuroQol-5 Dimensions five-level version (EQ-5D-5L)[54] and Short Form questionnaire-12 items (SF-12).[55]
- Functional impairment – Oswestry Low Back Pain Disability Questionnaire[56] and Pain Self-Efficacy Questionnaire (PSEQ).[57]
- Satisfaction with treatment (after treatment given) – NRS from 0 to 10, with 0 = 'extremely dissatisfied' and 10 = 'extremely satisfied'.
- Complications and adverse events – these were the subject of enquiry at visits and following procedures, as well as being spontaneously reported at any time. They were acted on as necessary and for the patients' benefit and were fully documented on case report forms and medical notes.
- Co-psychological well-being – Hospital Anxiety and Depression Scale (HADS),[58] Pain Catastrophizing Scale (PCS),[59] SF-12 and BPI.
- Health-care utilisation and costs and impact on productivity –Stanford Presenteeism Scale (SPS) 6,[60] self-reported measures of sickness absence over the previous 3 months and health-care utilisation in the form of hospital visits, treatments and medications. These data were collected at each outcome visit on the case report form.

TABLE 2 Schedule of assessments

Assessment	Prescreening	Visit 1	2	3	4 (6 weeks after injections ± 2 weeks)	5 (3 months after injections ± 2 weeks)	6 (6 months after injections ± 2 weeks)
Informed consent		✗					
Targeted physical examination	✗	✗					
Inclusion/exclusion criteria fulfilled		✗	✗	✗	✗	✗	✗
Medical history recorded		✗					
Demographic data recorded		✗					
Drug history recorded		✗	✗	✗	✗	✗	✗
Breakthrough analgesia recorded				✗	✗	✗	✗
Adverse events			✗	✗	✗	✗	✗
Outcome questionnaires		✗			✗	✗	✗
Expectation of benefit scale		✗					
BPI (Short Form)		✗			✗	✗	✗
SF-MPQ-2		✗			✗	✗	✗
EQ-5D-5L		✗			✗	✗	✗
SF-12		✗			✗	✗	✗
Oswestry Low Back Pain Disability Questionnaire		✗			✗	✗	✗
PSEQ		✗			✗	✗	✗
HADS		✗			✗	✗	✗
Pain Catastrophizing Scale		✗			✗	✗	✗
SPS 6		✗			✗	✗	✗
Satisfaction with treatment scale					✗	✗	✗

Adverse events

Adverse events were assessed by a blinded subinvestigator at each visit and an adverse event form was completed as necessary (see *Appendix 8*). Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered; an adverse reaction is an untoward and unintended response in a subject to an investigational medicinal product (IMP) that is related to any dose administered to that subject. A serious adverse event or reaction results in death, is life-threatening, requires inpatient hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect. A suspected unexpected serious adverse reaction is any serious adverse event that is both suspected to be related to the IMP and unexpected.

Adverse events not already identified locally were recorded at each trial visit and managed in accordance with the sponsor's requirements. Serious adverse events were reported to the JRMO by the investigators within 24 hours of the research team becoming aware of them and causality and expectedness were confirmed by the Chief Investigator, as the sponsor's medical representative.

Study management and committees

The Trial Management Group (TMG) was responsible for the overall management of the project and included all co-applicants and members of the study research team. A Trial Steering Committee (TSC) provided independent advice and support to the study and aimed to report to the funder on study progress. It was chaired by an independent clinician with experience of pain trials. A Data Monitoring Committee (DMC) had access to unblinded data and made recommendations to the TSC on whether there were any ethical or safety reasons why the trial should not continue. It included independent members who were all experts in pain medicine.

Patient and public involvement

Patients with personal experience of LBP collaborated in the early stages of study design, for example advising on the acceptability of study visits and the outcome questionnaires. The questionnaires were tested on patients presenting to the multidisciplinary pain clinics and were deemed to be acceptable. Patient representatives were invited to attend the TSC meetings; however, there was no patient or public involvement in the management or running of the trial beyond the initial set-up stage.

Statistical analysis

Analyses were conducted in accordance with the International Conference on Harmonisation (ICH) statistical guidelines for clinical trials[61] and the Consolidated Standards for Reporting Trials (CONSORT) reporting checklist for trials.[62] As this was a feasibility study, it was not planned to formally inferentially test differences in outcomes or costs between or within the groups. Mean recruitment and attrition rates were calculated with 95% confidence intervals (CIs). Means and SDs for all outcomes for the two groups at baseline and at the follow-up visits were reported. A detailed statistical analysis plan was prepared by the study statistician (RST) prior to any data analysis. Analyses were performed blinded to group allocation using Stata® 14.2 (StataCorp LP, College Station, TX, USA).

Health economics analysis

A health economics analysis plan was developed in collaboration with the study's health economist and statistician. A formal economic analysis was not proposed (as this was a feasibility study). Any outcomes from this feasibility study would be used in the design of the definitive study. In particular, the health economics analysis looked at the ability to collect the outcomes proposed for the main trial and to inform a robust framework to assess the cost-effectiveness of lumbar FJIs for persistent non-specific LBP for a future definitive randomised controlled trial.

The resources used in the delivery of the intervention and sham procedure were calculated from the case report forms and in consultation with the trial team. Health-care resource use was captured through administration of specific questions to trial participants at each assessment, with responses recorded on case report forms, with a focus on collecting data on the most relevant and important drivers of health resource use and costs. Published national costs were used to calculate the costs of delivering each treatment arm. A summary of the costing methods employed are presented in *Appendix 9*. In addition,

a literature review was conducted to review the scope and quality of the current economic evidence base for the use of FJIs in patients with non-specific LBP (see *Appendix 9*).

Descriptive analyses of the outcomes were used to report utilities based on the relevant tariff for each of the health-related quality-of-life outcomes. Economic outcomes were measured using the EQ-5D-5L (the preferred approach of the study team and for NICE decision-making) and the Short Form questionnaire-6 Dimensions (SF-6D[63]), used as a means of calculating utilities from the SF-12. A descriptive analysis of the health-related quality of life outcomes was summarised and was to provide estimates of quality-adjusted life-years (QALYs) gained as a result of receiving the intervention within the study period.

Summary of changes to the study protocol

The minor and major amendments made to the protocol over the duration of the study are detailed in *Appendix 10*.

Chapter 3 Results

Screening and recruitment

It was originally planned to screen and recruit participants across three centres; however, given the delays in study set-up, the funder directed that screening and recruitment take place at one centre only. The timelines of the study and the reasons for the delays are presented at the end of this chapter.

Recruitment began at Barts Health NHS Trust on 20 January 2016 and was terminated on 30 September 2016. As shown in *Figure 2*, during this time 628 patients referred to the recruiting clinics by their GP with non-specific LBP were screened for eligibility to enter the study. Of the 50 patients who met the inclusion criteria, 16 agreed to take part in the study and 11 received the diagnostic test for facet-joint disease. Nine participants had a positive response and were randomised to receive either lumbar FJIs with steroid or a sham procedure. The target sample size in each centre was 20 participants. The actual participant screening-to-recruitment ratio was 70 : 1 (628 : 9), which contrasts with an expected prestudy ratio of 17 : 1 (1000 : 60). The recruitment rate varied between zero and four patients per month (median two participants per month (*Table 3*).

The reasons for screening failure are detailed in *Table 4*. The greatest proportion of patients was screened from the pain clinics at St Bartholomew's Hospital, with a screened/recruited fraction of 1.69% (*Table 5*). Although only 16 patients were screened from the community pain clinic at the Essex Lodge GP surgery in Plaistow, East London, the screened/recruited fraction was higher at 12.5%. No participants were recruited from the spinal orthopaedic clinic at The Royal London Hospital or from the pain clinics at Whipps Cross University Hospital and Mile End Hospital.

Nine out of the 11 enrolled participants had a positive response to the diagnostic lumbar facet medial branch nerve block (82%, 95% CI 48% to 98%).

Adherence to allocated treatment

Facet-joint active and placebo injection

All the participants received their randomised procedure as planned and no problems with the injections were reported. None of the participants received any additional interventional pain procedures during their time in the study.

Combined physical and psychological programme

All nine participants were invited to attend a CPP programme after they had received their randomised procedure. Three physiotherapy-led CPP programmes took place between study months 12 and 20, with four participants in the first group, three in the second group and two in the final group. Six of the nine (67%) participants successfully completed the CPP programme, defined in the protocol as having attended at least four out of the six sessions. The median number of CPP programme sessions attended was four. One participant attended the initial CPP programme assessment but did not attend the programme because of illness during that period and another participant was unable to attend the CPP programme for personal reasons. A third participant did not attend the CPP programme because of unplanned overseas leave.

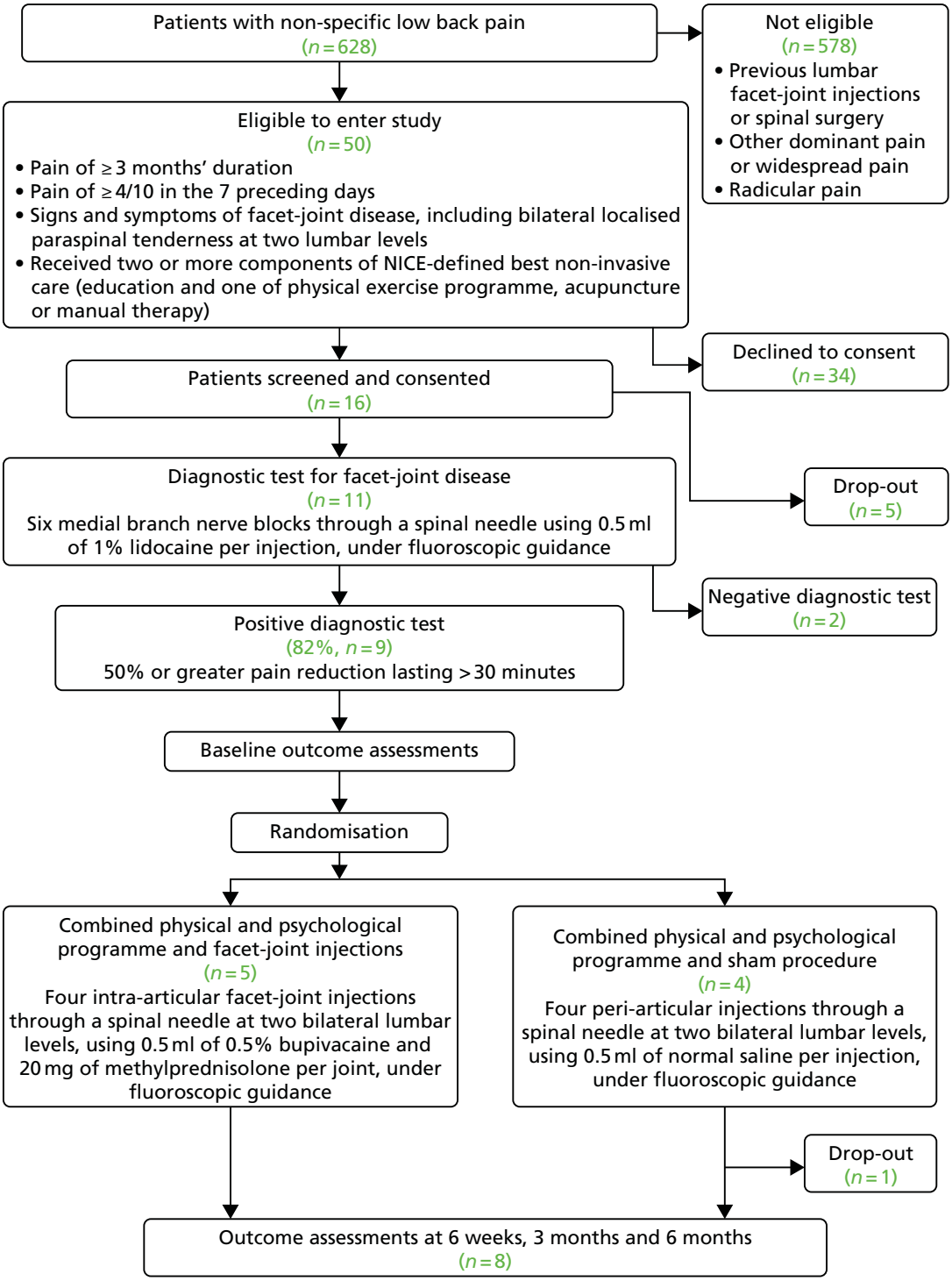

FIGURE 2 Consolidated Standards for Reporting Trials (CONSORT) flow diagram showing the flow of participants through the trial.

TABLE 3 Screening and recruitment by month

	Recruiting month									
Outcome	1	2	3	4	5	6	7	8	9	Total
Recruited	1	4	2	0	2	2	0	2	3	16
Screened	8	26	6	37	18	46	78	209	200	628

TABLE 4 Reasons for screening failure

Reasons	Number of patients
Previous lumbar FJIs	192
Previous lumbar FJIs	163
Previous lumbar FJIs and no previous physiotherapy	3
Previous lumbar FJIs and radiofrequency denervation	18
Previous lumbar FJIs or radiofrequency denervation and aged > 70 years	8
Other dominant pain or widespread pain	92
Radicular pain	64
Aged > 70 years[a]	42
Aged > 70 years	29
Previous lumbar FJIs or radiofrequency denervation and aged > 70 years	8
Aged > 70 years and has radicular pain	12
Aged > 70 years and has widespread pain	1
Other reasons for not meeting inclusion/exclusion criteria	36
Did not wish to take part	34
Previous major trauma to the lumbar spine	29
'Red flag' signs	29
Previous lumbar spinal surgery	25
Study team unable to contact	17
Already taking part in another study	12
Limited or no English language	11
Active neoplastic disease	7
No previous physiotherapy	7
Morbid obesity (body mass index of ≥ 35 kg/m^2)	7
Learning difficulties or known mental health illness	5
Known history of substance abuse	2
Aged < 18 years	1

a Some participants were in more than one category.

TABLE 5 Location of screening clinics at Barts Health NHS Trust

Clinic location	Number of patients		Screened/recruited fraction (%)
	Screened for eligibility	Randomised	
Pain clinic, St Bartholomew's Hospital	413	7	1.69
Spinal orthopaedic ('fracture') clinic, The Royal London Hospital	180	0	0
Community pain clinic, Essex Lodge GP surgery	16	2	12.5
Pain clinic, Whipps Cross Hospital	12	0	0
Tower Hamlets Persistent Pain Services, Mile End Hospital	7	0	0

Study dropout and attrition

Of the 16 patients recruited and who consented to take part in the study, five withdrew before they received their diagnostic injections (although all completed the baseline assessment questionnaires). One patient already had lumbar FJIs booked for a future date and two changed their mind about taking part (one for personal reasons and one for family reasons). Two were unable to attend for the injections as the study dates were not suitable for them.

Of the nine participants who were randomised, eight completed the study (defined as having completed the final set of questionnaires 6 months after the randomised procedure), resulting in an 11% (95% CI 0.2% to 48%) attrition rate. The expected attrition rate was 20%. Six study deviations were recorded: three participants did not complete the CPP programme and three participants did not complete all of the questionnaire sets (*Figure 3*). A 'study deviation' was defined as a participant who did not attend a study visit or CPP programme session but who did not drop out of the study completely.

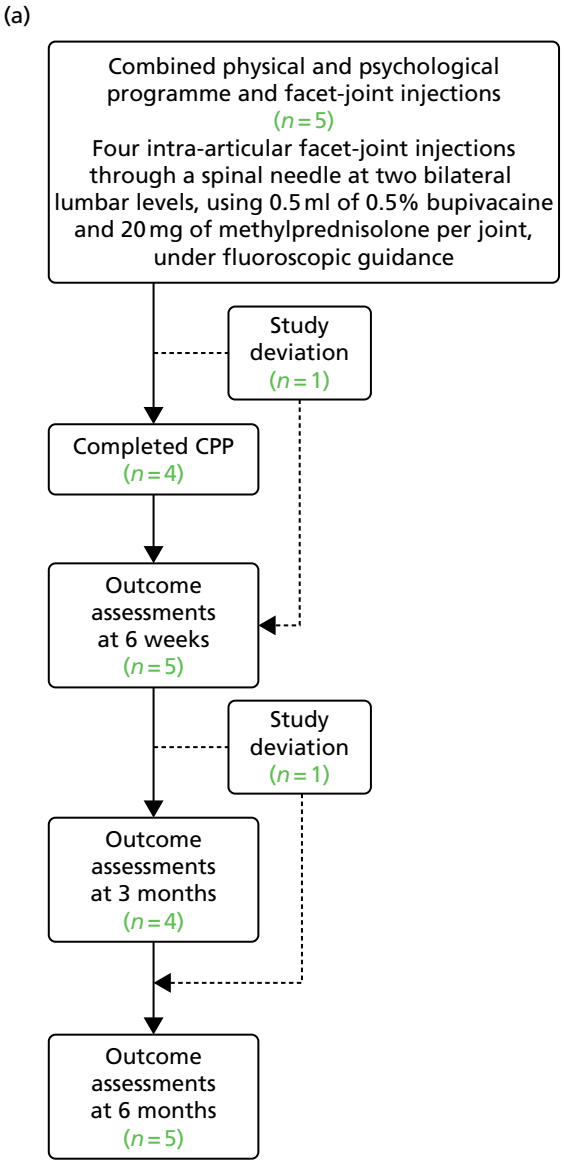

FIGURE 3 Flow diagram showing the study deviations and dropouts during the study. (a) Combined physical and psychological programme and facet-joint injections; and (b) combined physical and psychological programme and sham procedure. (*continued*)

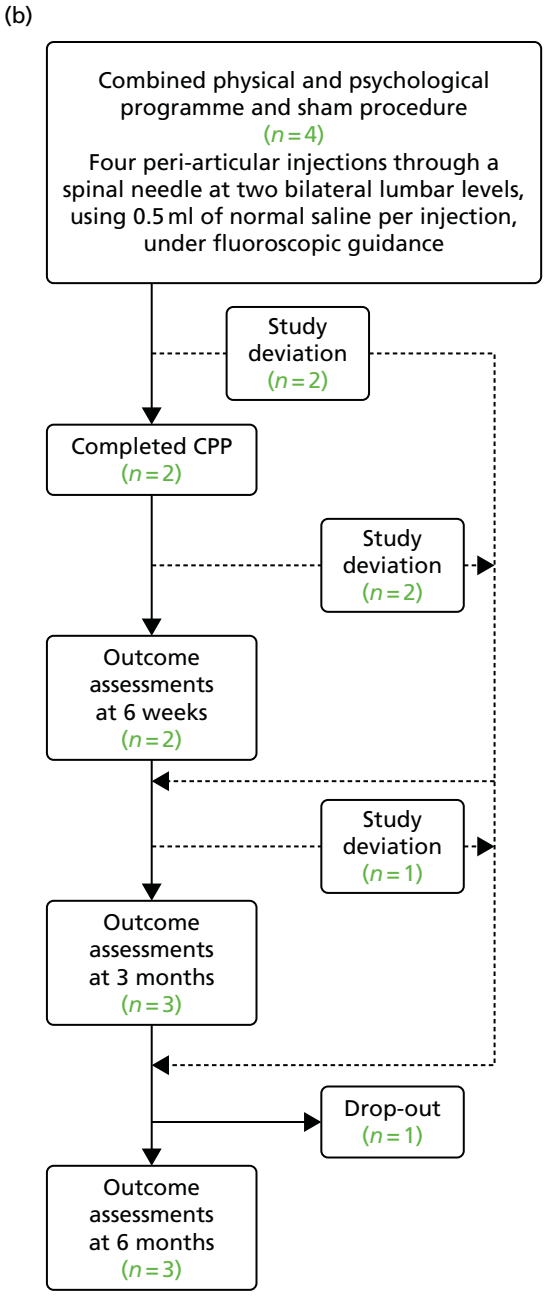

FIGURE 3 Flow diagram showing the study deviations and dropouts during the study. (a) Combined physical and psychological programme and facet-joint injections; and (b) combined physical and psychological programme and sham procedure.

There were low levels of missingness of within-questionnaire data, as shown in *Appendix 11*. This is summarised in *Table 6*.

Baseline characteristics and outcomes

The mean age of eligible participants was 45 years, with a similar proportion of males and females. Six out of 14 participants (43%) were not working at baseline (*Table 7*).

TABLE 6 Data missingness, CPP programme attendance and allocation groups

Participant number	Questionnaires completed				Number of CPP programme sessions attended	CPP programme group	Randomisation group
	Baseline	6 weeks	3 months	6 months			
1	Y	Y	Y	Y	5	1	Intervention
2	Y	N	N	Y	0	1	Sham
3	Y	Y	Y	Y	6	1	Sham
4	Y	Y	Y	Y	4	1	Intervention
5	Y	Y	Y	Y	6	2	Sham
6	Y	Y	N	Y	0	2	Intervention
7	Y	Y	Y	Y	5	2	Intervention
8	Y	Y	Y	N	0	3	Sham
9	Y	Y	Y	Y	4	3	Intervention

N, no; y, yes.

TABLE 7 Participant characteristics for all eligible and randomised participants

Characteristic	All eligible ($N = 16$[a])	Not randomised ($N = 7$)	Randomisation group	
			Sham ($N = 4$)	Intervention ($N = 5$)
Age (years), mean (SD)	44.8 (13.2)	44.4 (14.3)	50.5 (14.4)	40.8 (11.5)
Sex (male), *n* (%)	9 (56)	2 (29)	2 (50)	3 (60)
BMI (kg/m^2), mean (SD)	27.0 (5.1)	29.9 (5.1)	29.6 (4.7)	27.7 (5.6)
Baseline pain (0–10 VAS), mean (SD)	8.5 (1.5)	8.0 (1.7)	9.5 (1.0)	8.4 (1.5)
Duration of pain (months), mean (SD)	71.9 (88.7)	46.0 (53.6)	51.0 (46.3)	124.8 (135.9)
Location of pain, *n* (%)				
Bilateral	12 (75)	5 (71)	3 (75)	4 (80)
Unilateral	4 (25)	2 (29)	1 (25)	1 (20)
Aware of pain (years), mean (SD)	6.8 (7.6)	5.2 (4.6)	4.2 (3.9)	10.4 (11.3)
Description of health, *n* (%)				
Excellent	0 (0)	0 (0)	0 (0)	0 (0)
Very good	1 (7)	0 (0)	0 (0)	0 (0)
Good	9 (64)	3 (60)	3 (75)	1 (20)
Fair	1 (7)	1 (20)	0 (0)	3 (60)
Poor	3 (21)	1 (20)	1 (25)	1 (20)
Work status, *n* (%)				
Full time	7 (50)	1 (17)	2 (50)	4 (80)
Part time	1 (7)	0 (0)	1 (25)	0 (0)
Not working	4 (29)	3 (50)	0 (0)	1 (20)
Other	2 (14)	2 (33)	1 (25)	0 (0)

TABLE 7 Participant characteristics for all eligible and randomised participants (*continued*)

Characteristic	All eligible ($N = 16$[a])	Not randomised ($N = 7$)	Randomisation group	
			Sham ($N = 4$)	Intervention ($N = 5$)
Illness caused participant to stop working, *n* (%)				
Yes	10 (71)	1 (20)	3 (75)	3 (60)
No	4 (29)	4 (80)	1 (25)	2 (40)
Missed work days, mean (SD)	13.5 (31.1)	0 (0)	30.0 (52.0)	4.5 (3.7)
Level of activity prior to procedure, *n* (%)				
Hard manual	2 (29)	0 (0)	1 (33)	1 (33)
Lifting	1 (14)	1 (100)	0 (0)	0 (0)
Walking	0 (0)	0 (0)	0 (0)	0 (0)
Sedentary	4 (57)	0 (0)	2 (66)	2 (66)
Current smoker, *n* (%)				
Yes	11 (79)	2 (40)	0 (0)	1 (20)
No	3 (21)	3 (60)	4 (100)	4 (80)
Alcohol (units per week), mean (SD)	0.7 (1.1)	0.6 (1.3)	0.5 (1.0)	1.0 (1.2)
Exercise per week, *n* (%)				
> 5 days	2 (14)	0 (0)	1 (25)	1 (20)
3–5 days	1 (7)	1 (20)	0 (0)	0 (0)
1–2 days	5 (36)	1 (20)	1 (25)	3 (60)
< 1 day	6 (43)	3 (60)	2 (50)	1 (20)

VAS, visual analogue scale.
a Not all eligible and randomised participants contributed data.

Baseline patient-reported outcomes indicated a population with substantial levels of pain [mean 8.5 on a 0–10 visual analogue scale (VAS)] that was predominantly bilateral (12/16, 75%) and which had a mean duration of 72 months (see *Table 7*). In terms of the primary and secondary outcomes, high baseline levels of disability and mental ill health and poor overall health-related quality of life were seen (*Tables 7* and *8*).

Given the small number of participants randomised, not unexpectedly there was evidence of imbalance in participant characteristics and patient-reported outcomes between the two groups at baseline (see *Table 8*).

Primary and secondary outcomes at follow-up

Given the feasibility nature of the study and the small number of participants randomised, the primary and secondary outcomes at 6 weeks' and 3 and 6 months' follow-up are presented descriptively, with no inferential between or within comparisons undertaken or reported (*Table 9*).

Adverse events

Three study participants reported adverse events, with two serious events reported by one participant. All three participants reported a flare-up of their LBP, which resolved (*Table 10*).

TABLE 8 Primary and secondary outcomes at baseline

Outcome	All eligible ($n = 16$[a])	Not randomised ($n = 7$)	Randomisation group, mean score (SD)	
			Sham ($n = 4$)	Intervention ($n = 5$)
BPI (0–10)				
Worst pain	8.5 (1.7)	9.0 (0.9)	9.3 (1.5)	7.2 (2.2)
Least pain	6.0 (2.7)	6.2 (2.3)	6.0 (2.7)	6.0 (3.5)
Average pain	7.4 (1.5)	7.7 (1.5)	7.5 (1.9)	7.0 (1.6)
Pain now	6.5 (2.8)	5.2 (2.9)	8.0 (2.3)	6.8 (2.8)
Pain severity	7.1 (1.6)	7.0 (0.8)	7.7 (1.7)	6.8 (2.4)
General activity	7.7 (2.5)	7.7 (2.6)	9.3 (1.5)	6.6 (1.2)
Mood	6.9 (2.2)	6.7 (2.4)	7.0 (2.4)	7.0 (4.8)
Walking ability	6.3 (2.8)	6.2 (2.3)	5.5 (2.0)	7.0 (2.7)
Normal work	8.1 (2.2)	8.5 (2.1)	8.5 (1.7)	7.2 (2.9)
Relations	6.2 (2.5)	5.3 (3.3)	6.5 (1.9)	7.0 (4.8)
Sleep	7.1 (3.0)	5.8 (3.5)	8.8 (1.9)	7.4 (3.0)
Enjoyment	7.4 (3.0)	6.8 (3.9)	8.3 (1.7)	7.4 (3.0)
Interference	7.1 (3.9)	6.7 (4.7)	7.7 (1.8)	7.1 (2.4)
SF-MPQ-2				
Continuous pain	5.2 (2.0)	5.6 (0.9)	4.5 (3.0)	5.3 (2.2)
Intermittent pain	4.4 (2.5)	4.7 (2.4)	4.2 (2.6)	4.3 (3.1)
Neuropathic pain	2.7 (1.9)	2.7 (2.2)	2.1 (1.8)	3.2 (1.7)
Affective descriptors	4.0 (2.6)	3.9 (2.8)	2.0 (1.5)	5.6 (2.4)
Total	4.1 (1.7)	4.2 (1.5)	3.3 (2.0)	4.5 (2.0)
Oswestry Low Back Pain Disability Questionnaire				
Total	49.2 (17.6)	55.8 (19.4)	48.8 (19.9)	43.0 (15.0)
PSEQ				
Total	21.3 (12.8)	16.5 (15.8)	27.0 (7.7)	22.6 (12.2)
SF-12				
PCS	33.5 (5.8)	34.5 (5.8)	32.7 (6.0)	33.1 (6.7)
MCS	35.7 (11.2)	34.7 (14.7)	43.4 (10.0)	30.4 (4.6)
HADS				
Anxiety	10.1 (4.0)	10.3 (5.2)	7.5 (3.4)	12.0 (1.2)
Depression	9.7 (4.1)	11.0 (4.8)	6.8 (3.9)	10.4 (3.4)
Pain Catastrophizing Scale				
Rumination	12.5 (3.9)	11.7 (4.9)	11.5 (4.0)	14.2 (2.5)
Magnification	7.1 (3.3)	6.8 (3.3)	6.3 (4.3)	8.0 (3.2)
Helplessness	15.7 (4.4)	16.3 (4.8)	11.7 (4.4)	18.0 (4.8)
Total	35.2 (11.1)	34.8 (11.7)	29.5 (12.3)	40.2 (9.0)
EQ-5D-5L index	0.41 (0.30)	0.43 (0.29)	0.40 (0.21)	0.39 (0.35)
Expectation of benefit	3.3 (1.7)	2.7 (2.4)	3.5 (0.6)	3.8 (1.1)

MCS, mental component summary; PCS, physical component summary.
a For some outcomes only 14 participants contributed data.

TABLE 9 Summary of primary and secondary outcomes at all follow-up points

Outcome	Follow-up time point, mean score (SD)					
	6 weeks		3 months		6 months	
	Sham group ($n = 2$)	Intervention group ($n = 5$)	Sham group ($n = 3$)	Intervention group ($n = 4$)	Sham group ($n = 3$)	Intervention group ($n = 5$)
BPI (0–10)						
Worst pain	5.0 (2.8)	7.8 (1.9)	7.3 (3.0)	7.8 (1.7)	6.3 (4.7)	6.0 (3.5)
Least pain	4.0 (1.4)	5.2 (2.5)	7.0 (3.6)	5.3 (2.2)	5.3 (4.5)	5.0 (2.8)
Average pain	4.5 (2.1)	6.2 (2.5)	6.0 (2.6)	6.3 (2.5)	5.3 (4.5)	5.6 (2.6)
Pain now	5.0 (2.8)	6.6 (2.1)	6.3 (3.0)	5.8 (2.1)	6.0 (4.6)	5.2 (3.7)
Pain severity	4.6 (2.3)	6.5 (2.1)	6.7 (3.0)	6.3 (2.1)	5.8 (4.5)	5.5 (3.1)
General activity	5.0 (4.2)	6.2 (2.4)	6.7 (2.3)	7.3 (1.9)	6.0 (5.3)	5.6 (3.6)
Mood	4.5 (2.1)	7.2 (1.9)	7.0 (3.6)	7.8 (2.1)	5.3 (5.0)	5.6 (3.6)
Walking ability	4.0 (1.4)	7.2 (2.6)	5.3 (1.5)	6.0 (2.9)	4.3 (4.9)	5.0 (4.6)
Normal work	5.5 (0.7)	7.2 (2.6)	6.0 (2.0)	6.8 (2.8)	5.0 (5.0)	6.0 (4.7)
Relations	3.5 (2.1)	6.2 (3.4)	5.7 (4.0)	7.5 (1.9)	4.0 (5.3)	5.2 (3.2)
Sleep	6.5 (4.9)	8.0 (1.9)	7.0 (2.6)	6.3 (2.9)	4.3 (5.1)	6.0 (4.7)
Enjoyment	4.5 (2.1)	7.6 (2.3)	7.7 (2.5)	7.0 (2.2)	4.7 (4.7)	6.2 (3.3)
Interference	4.8 (2.1)	7.1 (1.9)	6.5 (2.4)	6.9 (2.2)	4.8 (4.9)	5.7 (3.8)
SF-MPQ-2						
Continuous pain	3.8 (3.2)	4.9 (3.1)	6.3 (3.4)	3.9 (1.4)	4.1 (3.7)	3.3 (2.6)
Intermittent pain	4.4 (3.7)	3.7 (2.5)	4.9 (3.0)	3.7 (3.5)	3.5 (2.9)	3.6 (3.8)
Neuropathic pain	1.7 (1.8)	4.0 (3.2)	2.5 (1.5)	2.0 (0.9)	3.6 (3.4)	3.0 (2.9)
Affective descriptors	4.4 (4.8)	4.6 (3.0)	5.6 (4.0)	5.4 (1.2)	2.5 (2.5)	3.7 (2.8)
Total	3.5 (3.3)	4.2 (2.3)	4.8 (2.6)	3.6 (1.5)	3.5 (2.9)	3.4 (2.8)
Oswestry Low Back Pain Disability Questionnaire						
Total	36.0 (17.0)	48.4 (20.2)	56.0 (14.4)	39.0 (9. 9)	42.6 (34.0)	39.9 (26.0)
PSEQ						
Total	33.5 (10.6)	21.2 (15.3)	27.7 (9.6)	31.8 (14.1)	28.3 (21.7)	33.2 (19.4)
SF-12						
PCS	38.8 (10.3)	33.7 (8.6)	38.5 (6.8)	40.8 (11.0)	34.4 (12.5)	39.5 (13.7)
MCS	43.6 (15.4)	31.3 (7.9)	35.7 (7.8)	37.8 (2.6)	47.2 (22.1)	38.1 (13.5)
HADS						
Anxiety	7.0 (1.4)	12.8 (4.4)	8.3 (3.8)	11.5 (4.6)	6.7 (5.7)	10.0 (3.9)
Depression	4.0 (4.3)	10.8 (6.7)	8.0 (3.5)	9.5 (5.5)	7.7 (8.1)	8.4 (7.1)
Pain Catastrophizing Scale						
Rumination	11.0 (1.4)	12.4 (4.9)	15.0 (1.0)	11.8 (4.8)	15.8 (3.8)	14.4 (5.5)
Magnification	8.0 (1.4)	6.6 (2.9)	10.3 (0.6)	5.0 (3.5)	19.5 (3.5)	13.8 (5.9)
Helplessness	14.0 (2.8)	15.0 (7.0)	13.7 (6.5)	15.0 (8.9)	16.7 (6.1)	15.5 (9.0)
Total	33.0 (5.6)	34.0 (14.0)	19.0 (6.6)	32.7 (17.2)	16.7 (7.6)	16.0 (7.4)
EQ-5D-5L index	0.67 (0.30)	0.43 (0.33)	0.42 (0.10)	0.62 (0.28)	0.60 (0.50)	0.51 (0.41)
Satisfaction	6.3 (3.8)	6.6 (0.9)	7.3 (1.2)	7.5 (0.6)	9.7 (0.6)	6.0 (2.1)

MCS, mental component summary; PCS, physical component summary.

TABLE 10 Summary of adverse events

Participant number	Description of adverse event	Relationship to IMP, as judged by the Principal Investigator	Seriousness of the adverse event, as judged by the Principal Investigator	Randomisation group
1	Flare-up of LBP after the randomised procedure	Expected reaction, related to the IMP	Not serious	Sham
4	Flare-up of LBP 5 months after the randomised procedure	Expected reaction, related to the IMP	Not serious	Intervention
7	Urinary incontinence	Unexpected reaction, not related to the IMP	Serious adverse event (required overnight stay in hospital)	Intervention
	Swelling at site of injections	Expected reaction, related to the procedure but not to the IMP	Serious adverse reaction (required overnight stay in hospital)	
	Flare-up of LBP after the randomised procedure	Expected reaction, related to the IMP	Not serious	
	Flare-up of LBP 5 months after the randomised procedure	Expected reaction, related to the IMP	Not serious	

Blinding to treatment allocation

To test the fidelity of blinding, participants were asked to guess which allocation group they had been randomised to, prior to being unblinded at the end of the study. Only one out of eight participants who completed the study correctly guessed their allocation group. The blinded outcome assessor correctly guessed the allocation group for four of the nine participants.

Health economics analysis

Given the importance of health economics evidence in informing decision-making, the incorporation of a health economics work package as part of a feasibility study can inform the delivery of a robust trial in the future, evaluating clinical effectiveness and cost-effectiveness. The main objective of the health economics analysis was to assess the feasibility of collecting data and produce an appropriate framework for a future full economic evaluation. This included a description of the main resource and cost drivers during the patient pathway in delivering the intervention and an assessment of collecting resource use information based on a resource use questionnaire devised for the feasibility study. An assessment of the performance of two preference-based health-related quality of life measures – the SF-12 (SF-6D)[55] and EQ-5D-5L[54] – within the feasibility study was also proposed in the original health economics analysis plan.

We intended to present both of the scores from the full EQ-5D (EuroQol-5 Dimensions) questionnaire, that is, the EQ-5D-5L descriptive system and the EQ-5D VAS, to present a comprehensive picture of patient-reported outcomes. Patients are asked to assess their health state on five dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression – using five levels ranging from 'no problems' to 'severe problems'. A single summary index is obtained by applying a formula that attaches weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D health states from a general population sample in the UK.[64] The EQ-5D VAS is a thermometer-type vertical 20-cm scale with the end points of best imaginable health state (at the top) and worst imaginable health state (at the bottom) having numerical values of 100 and 0 respectively. This is a self-rated valuation and represents the respondents' views of their health state and how it has affected their life on the day.

The utilities derived from the EQ-5D-5L and SF-6D were converted into QALYs to present a profile of QALY gains/losses over time.

As this was not a full trial, no inferential statistical comparisons of health-related quality of life or service use between the intervention group and the control group were planned. Instead, the focus was on reporting descriptive findings for the two groups at baseline and at the follow-up points to inform a suitable framework for a future economic evaluation if the findings from the feasibility study could be used to inform a future definitive study.

For the feasibility study, the perspective adopted was that of the UK NHS, focusing on primary and secondary resource use. However, given the impact of back pain on the patient and wider society (e.g. because of reduced/lost work productivity), a preliminary assessment of employment-related outcomes using the SPS 6[60] was reported as part of the trial outcomes. The economic analysis was conducted using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA).

Literature review

As part of the assessment of the feasibility of undertaking a future full economic analysis, a structured, rapid review of the literature was undertaken (see *Appendix 9*). This rapid review identified two partial economic evaluations (costs of FJIs)[65,66] and one study that evaluated health-related quality of life.[37] We found limited economic evidence, with no cost-effectiveness studies identified of diagnostic or therapeutic FJIs. In undertaking any future trial, the feasibility of considering longer-term horizons should be fully assessed, for example whether a model-based analysis can be conducted to robustly extrapolate beyond the trial horizon, based on the suitability and quality of external literature sources.

Identification of the main resource and cost drivers associated with the delivery of facet-joint injections

A descriptive profile of resource use and costs was developed in consultation with the trial team to understand the opportunity costs associated with the delivery of the intervention. These were valued in Great British pounds in 2016 prices based on published unit costs or other literature sources.[10,67–69] The resource use reported at each of the trial visits was assessed with regard to whether it represented (1) research costs (which would be identified and excluded from any intervention costs), (2) costs attributed to routine usual NHS care or (3) opportunity costs (e.g. associated with additional staff time in managing a patient following FJIs) as a result of the intervention.

The intervention costs were considered in the following stages:

- identification and screening of patients suitable for treatment (entry into the trial)
- delivery of the intervention or sham procedure
- delivery of the CPP programme
- follow-up assessments.

The identification and screening of patients occurred during a routine consultant-led outpatient pain clinic appointment. The associated unit cost per patient was recorded as £148.03 for both groups.[67] Delivery of the intervention or sham procedure occurred at a routine day surgery unit at a cost of £691 per patient. The procedure was identified from the NHS national schedule of reference costs for 2015–16[68] as an Injection of Therapeutic Substance into Joint for Pain Management (currency code AB19Z).

Delivery of the CPP programme had a mean cost of £2500 per patient.[70] However, as this programme was delivered to both groups, we excluded the CPP programme costs from the final cost analysis.

There were three follow-up assessments. Two assessments/data collection sessions were research-based, nurse-led appointments and were not included in the costs. The 6-month follow-up appointment was

conducted by a consultant at an outpatient pain clinic as part of routine aftercare post procedure at a cost of £148.03 per patient for both groups.[69]

Health resource use

An assessment of the feasibility of gathering appropriate resource use data from a patient sample was a major component of this evaluation. The resource use measure was developed by the clinical team based on standard clinical practice for the management of LBP and included questions on primary and secondary care resource use (e.g. hospital admissions, outpatient visits, GP surgery visits and medication use).

Feasibility of collecting resource use data

The resource use questionnaire was completed by the trial research assistant during scheduled visits to a nurse-led outpatient pain management clinic and took approximately 60 minutes per visit to complete. Although these are 'research' costs, the cumulative impact of collecting data will add to the costing of the time/resources for any future trial.

The focus was on collecting information on consultations with the NHS health-care professionals who would most likely be involved in the management of LBP. All costs were valued in Great British pounds using a price year of 2016. *Table 23* (see *Appendix 9*) summarises this resource use. As the trial period was < 12 months, no discounting was applied to costs or outcomes. An additional question allowed patients to report any other resources used outside of the main categories; however, no other reported resource items were recorded.

Data on hospital contacts collected via the resource use questionnaire was compared with the data collected on adverse events and serious adverse events to ensure that there was no overlapping of data collected and, therefore, no double-counting of resource use. Prior to the analysis, appropriate decision rules were put in place for the costing of hospital admissions. If a patient was reported as having been admitted to hospital during the past 4 weeks, as a result of a serious adverse event, this was classified as an emergency hospital admission (non-elective inpatient stay). If (in an expected minority of patient cases) a hospital admission was for a condition unrelated to LBP, the reason for the unrelated hospital admission was recorded but the hospital admission was not included in the analysis.

The findings from the trial identified neither serious adverse events resulting in a hospital admission nor any other hospital admissions during the trial period. When documented adverse events were examined ($n = 3$ participants accounting for six health-care contacts), no additional impact on resource use was identified as one of the following: (1) already documented within the resource use questionnaire; (2) no further action or impact on resource use was documented; or (3) the adverse event was unrelated to the intervention. In two cases an adverse event was reported by the patient but no further information was available.

The resource use questionnaire collected information on current prescribed analgesics and any other medications at baseline. At the three follow-up time points, information on current analgesics and other medications was also collected along with any changes in medication during the follow-up period. The specific dates that prescriptions were issued, including the dates that any changes in medication occurred, were unknown because medications were prescribed by the patients' GPs rather than by the trial team. Medication reported in the 'other' medication category that was not related to the treatment of LBP was excluded following examination of the data by the trial Chief Investigator. The costs of medication were then compiled for each time point and summated to give a total medication cost per group.

Resource use and costs

Table 11 summarises the NHS resource use for participants from baseline to 6 months' follow-up. Overall, the total number of primary care visits was the same across the groups over the time period of the trial (seven GP visits recorded with a total cost per group of £252).[67] No emergency department admissions or hospital inpatient admissions (either elective or emergency) were recorded in either group. One outpatient appointment was recorded in the intervention group (received FJIs) at a cost of £148.[68]

TABLE 11 NHS resource use and costs by NHS sector between baseline and 6 months' follow-up

	Visits		Total costs (aggregate of all follow-up time points) (£)	
Consultations for LBP	Sham group ($n = 4$)	Intervention group ($n = 5$)	Sham group ($n = 4$)	Intervention group ($n = 5$)
Total GP visits				
Number of visits/cost	7	7	252.00	252.00
Mean (SD)	1.75 (1.71)	1.4 (2.19)	63.00 (61.48)	50.40 (78.87)
Min., max.	0, 4	0, 5	0, 44.00	0, 180.00
Total outpatient pain clinic appointments				
Number of visits/cost	0	1	0	148.03
Mean (SD)				
Min., max.				
Total hospital emergency inpatient admissions				
Number of visits/cost	0	0	0	0
Mean (SD)				
Min., max.				
Total emergency department admissions				
Number of visits/cost	0	0	0	0
Mean (SD)				
Min., max.				
Total medication costs				
Total cost			48.83	562.51
Mean (SD)			12.21 (11.31)	112.50 (81.25)
Min., max.			1.21, 29.63	29.63, 231.76

Max., maximum; min., minimum.

The main numerical differences between the two groups occurred for medication use, with a total cost of £48.83 (mean cost £12.21 per participant; SD £11.31) in the sham group and £562.51 (mean cost £112.50 per participant; SD £81.25) in the intervention group, a mean difference of £100 per participant. Further details of the medication use over each time point are provided in *Table 12*.

Although there are limitations of the analysis associated with the highly skewed costs and small sample size, this suggests that a potential downstream effect of FJI is a subsequent increase in medication use and associated costs within primary care.

Table 13 provides an estimation of the total mean costs of the FJI intervention and the sham procedure. This shows that the FJI intervention was assessed as costing £118 more per patient than the sham procedure.

Outcomes

At baseline all nine patients completed the EQ-5D assessment. However, at the follow-up data collection points only six participants (two in the sham group and four in the intervention group) returned complete assessments across all three time points.

TABLE 12 Overall costs of prescribed analgesic medication after facet-joint treatment

Follow-up time period	Randomisation group	
	Sham ($n = 4$) (£)	Intervention ($n = 5$) (£)
From baseline to 6 weeks' follow-up (visit 4)		
Total	32.05	35.75
Mean (SD)	8.01 (12.04)	7.15 (12.68)
Min., max.	0, 25.78	0, 29.27
From 6 weeks' follow-up to 3 months' follow-up (visit 5)		
Total	4.25	129.63
Mean (SD)	1.06 (2.13)	25.93 (30.94)
Min., max.	0, 4.25	0, 77.95
From 3 months' follow-up to 6 months' follow-up (visit 6)		
Total	12.53	397.13
Mean (SD)	3.12 (3.82)	79.43 (58.95)
Min., max.	0, 7.75	23.25, 156.12
Total medication costs after treatment		
Total	48.83	562.51
Mean (SD)	12.21 (11.31)	112.50 (81.25)
Min., max.	1.21, 29.63	29.63, 231.76
Difference between groups		
Total cost difference	513.68	
Mean cost difference	100.29	

Max., maximum; min., minimum.

TABLE 13 Mean costs associated with the facet-joint intervention and the sham procedure

Mean cost	Randomisation group, mean (SD)		Mean cost difference
	Sham ($n = 4$)	Intervention ($n = 5$)	
Total cost (£)	75 (73)	193 (219)	The intervention is £118 more expensive per patient than the sham procedure

The baseline mean EQ-5D-5L and SF-6D utilities and EQ-5D VAS scores are presented in *Tables 14* and *15*, respectively, which compare the values for those patients who completed the assessments (complete cases) with the values for those who withdrew after completing the baseline assessments. As a point of reference, utilities from a UK population with LBP are presented.[71]

At baseline, there were numerical differences in baseline EQ-5D-5L utilities, with those lost to follow-up having very slightly numerically higher utilities than those in the sham and intervention groups (0.43 vs. 0.40 vs. 0.39). The minimum and maximum values indicate that there is potentially a wide range of scores and the potential for heterogeneity within the patient sample. Although appropriate caution must be exercised in the interpretation of these baseline scores, further examination of baseline differences in utilities should be examined in any future trial. Brazier *et al.*[71] reported that, on average, the SF-6D generates utility values that are higher than those generated using the EQ-5D-5L and this is also reflected in this trial sample. The SF-6D results show that those in the intervention group have a marginally higher utility score than those who withdrew after the baseline assessment and those who received the sham procedure (0.53 vs. 0.52 vs. 0.51).

TABLE 14 Mean EQ-5D-5L and SF-6D utility scores at baseline

Outcome	Randomisation group		Group lost to follow-up	Utilities by disease (lower back pain)[a]
	Sham	Intervention		
EQ-5D-5L utility score				
n	4	5	5	265
Mean (SD)	0.402 (0.209)	0.387 (0.355)	0.429 (0.362)	0.635 (0.266)
Min.	0.147	–0.068	–0.0004	–0.181
Max.	0.619	0.816	0.802	1.000
SF-6D utility score				
n	4	4	5	263
Mean (SD)	0.509 (0.068)	0.532 (0.073)	0.523 (0.064)	0.658 (0.144)
Min.	0.450	0.450	0.410	0.370
Max.	0.590	0.620	0.570	1.000

Max., maximum; min., minimum.
a A comparison of the EQ-5D and SF-6D utilities of patients with LBP conducted by Brazier *et al.*[71]

TABLE 15 Mean EQ-5D VAS score at baseline

EQ-5D VAS score[a]	Randomisation group		Group lost to follow-up ($n = 6$)
	Sham ($n = 4$)	Intervention ($n = 5$)	
Mean (SD)	58.75 (23.94)	45.60 (9.32)	47.67 (22.46)
Min.	25.0	38.0	20.0
Max.	80.0	60.0	80.0

Max., maximum; min., minimum.
a Ranging from 0 (worst health) to 100 (best possible health).

The EQ-5D VAS results showed a different picture, with VAS scores ranging from 45.60 in the intervention group to 47.67 in the group who withdrew after completing the baseline assessment and 58.75 in the sham group, again showing the potential for heterogeneity in the patient sample.

Stanford Presenteeism Scale 6 scores at baseline

Scores on the SPS 6 range from 6 to 30, with lower scores indicating lower presenteeism and higher scores indicating higher presenteeism.[60] Higher presenteeism scores are associated with decreased productivity and work quality. At baseline the sham group and the group lost to follow-up reported slightly higher scores of 15.8 and 15.2, respectively, with the intervention group having the lowest mean score of 14.4, as shown in *Table 16*.

Stanford Presenteeism Scale 6 scores at the follow-up assessments

After treatment, at the follow-up assessments, the sham group still had slightly higher presenteeism scores than those who received the intervention (*Table 17*). Although the intervention group showed a reduction in presenteeism score at the 6-week time point, both groups tended to report higher presenteeism scores after treatment than at baseline.

Comparison of utilities across assessment points

Table 18 summarises the utilities across the groups at the three follow-up points to 6 months using the EQ-5D-5L and SF-6D. It is important to acknowledge the impact of missing data, with two participants in the sham group missing data at the 6-week assessment, one participant from each group missing data at the 3-month assessment and one participant from the sham group missing data at the 6-month

TABLE 16 Stanford Presenteeism Scale 6 scores at baseline

	Randomisation group		
SPS 6 score	Sham ($n = 4$)	Intervention ($n = 5$)	Group lost to follow-up ($n = 5$)[a]
Mean (SD)	15.8 (3.8)	14.4 (5.5)	15.2 (3.1)
Min.	11.0	6.0	11.0
Max.	20.0	20.0	18.0

Max., maximum; min., minimum.
a One missing response.

TABLE 17 Stanford Presenteeism Scale 6 scores at follow-up

	Follow-up time point					
	6 weeks (visit 4)		3 months (visit 5)		6 months (visit 6)	
SPS 6 score	Sham group ($n = 2$)	Intervention group ($n = 5$)	Sham group ($n = 3$)	Intervention group ($n = 4$)	Sham group ($n = 3$)	Intervention group ($n = 5$)
Mean (SD)	19.5 (3.5)	13.8 (5.9)	16.7 (6.1)	15.5 (9.0)	16.7 (7.6)	16.0 (7.4)
Min.	17.0	7.0	10.0	7.0	8.0	6.0
Max.	22.0	22.0	22.0	26.0	22	24.0

Max., maximum; min., minimum.

TABLE 18 Mean utility scores at follow-up

	Follow-up time point					
	6 weeks (visit 4)		3 months (visit 5)		6 months (visit 6)	
Outcome	Sham group ($n = 2$)	Intervention group ($n = 5$)	Sham group ($n = 3$)	Intervention group ($n = 4$)	Sham group ($n = 3$)	Intervention group ($n = 5$)
EQ-5D-5L utility score						
Mean (SD)	0.675 (0.118)	0.433 (0.335)	0.418 (0.098)	0.617 (0.279)	0.597 (0.499)	0.520 (0.413)
Min.	0.592	0.013	0.352	0.204	0.021	0.018
Max.	0.758	0.762	0.531	0.802	0.893	0.841
SF-6D utility score						
Mean (SD)	0.708 (0.244)	0.452 (0.080)	0.557 (0.096)	0.561 (0.160)	0.622 (0.249)	0.615 (0.149)
Min.	0.540	0.380	0.470	0.410	0.370	0.450
Max.	0.880	0.570	0.660	0.730	0.860	0.820

Max., maximum; min., minimum.

assessment. Although the small sample size precluded any formal assessment of missing data, this highlights the importance of ensuring that outcomes are as complete as possible over the follow-up period and, when necessary, that there are appropriate decision rules to handle missing data (e.g. suitable imputation methods) for formal economic analysis in any future trial.

For the EQ-5D-5L, the sham group showed an increase in utility from 0.40 at baseline to 0.68 at 6 weeks. This declined at 3 months to 0.42 before increasing to 0.60 at 6 months, indicating small changes during the treatment and follow-up period. In the intervention group, the baseline score of 0.39 increased slightly to 0.43 at 6 weeks and 0.62 at 3 months and then declined to 0.52 at 6 months. Although no quantitative assessment (given the limitations of the data) can produce a reliable numerical magnitude of

effect, the direction of travel suggests that, overall, there are likely to be small effects on health-related quality of life. The SF-6D scores were, in the main, higher than the EQ-5D-5L scores. At 6 weeks' follow-up the sham group reported a considerably higher score than the intervention group (0.71 vs. 0.45). However, at 3 months' and 6 months' follow-up both groups reported the same utility scores: 0.56 at 3 months increasing to 0.62 by the end of the trial.

The mean EQ-5D VAS scores at follow-up are presented in *Table 19*. A similar pattern of missing data was seen. Overall, there were numerical differences between each time point in both groups, with the sham group showing a very slight improvement in VAS score from baseline to 6 weeks (58.75 vs. 60.00), a reduction in VAS score between 6 weeks and 3 months (60.0 vs. 43.33) and an improvement in VAS score from 3 months to 6 months (43.33 vs. 53.33). In contrast, the intervention group showed a decline from baseline to 6 weeks (45.60 vs. 38.33), an improvement between 6 weeks and 3 months (38.33 vs. 53.33) and a decline from 3 months to 6 months (53.33 vs. 45.00).

Changes in quality-adjusted life-years

Given the potential inclusion of a cost–utility analysis within a future economic analysis, the utilities derived from the EQ-5D-5L and SF-6D were translated into QALYs using the methodology outlined in *Appendix 9*. *Table 20* summarises the QALYs at each time point by group. With respect to the EQ-5D-5L, from baseline to 6 months the mean (SD) QALY gain was 0.31 (0.32) in the sham group and 0.28 (0.15) in the intervention group. The SF-6D produced slightly higher QALY gains at 6 months, with the sham group reporting a mean (SD) gain of 0.32 (0.076) and the intervention group reporting a mean (SD) gain of 0.30 (0.044).

In the health economics analysis plan, the original intention was to compare the psychometric properties of the EQ-5D-5L with those of the SF-6D using a similar set of analyses as reported by Mulhern *et al.*,[72] to inform the potential choice of preference-based measure of health-related quality of life in any future trial. However, given the limitations presented by the small sample size (and within this the further impact of missing data), this analysis could not be undertaken given that it did not meet any of the accepted criteria in terms of a sufficient sample size to conduct appropriate tests associated with assessing the reliability and validity of patient-reported outcomes.[73]

Health economics summary

The health economics results are purely descriptive and with such a small sample size we are appropriately cautious about drawing any conclusions. The incorporation of an early-stage assessment of the requirements and parameters for an economic analysis in a future trial has allowed a provisional assessment of these, with evidence from the feasibility study providing a useful basis for the development of a suitable framework. Because of the constraints presented, in-depth examination was not undertaken and the provisional assessments (e.g. early assessment of the intervention costs associated with FJIs) must be interpreted with caution. A key learning point was the need for health economics analysis to be embedded into the feasibility study to ensure that important insights and lessons can be used to develop

TABLE 19 Mean EQ-5D VAS scores at follow-up

	Follow-up time point					
	6 weeks (visit 4)		3 months (visit 5)		6 months (visit 6)	
EQ-5D VAS score	Sham group ($n = 2$)	Intervention group ($n = 3$)	Sham group ($n = 3$)	Intervention group ($n = 3$)	Sham group ($n = 3$)	Intervention group ($n = 5$)
Mean (SD)	60.00 (28.28)	38.33 (10.41)	43.33 (25.17)	53.33 (25.17)	53.33 (47.26)	45.00 (29.15)
Min.	40	30	20	30	0	10
Max.	80	50	70	80	90	80

Max., maximum; min., minimum.
The mean EQ-5D VAS scores shown above are derived from the VAS health scale. When a VAS score was missing the BOX health scale[54] was used as a substitute. If the VAS and the BOX scale scores differed, the mean of both scores was used as a substitute.

TABLE 20 Mean QALY gain from baseline to 6 months

Outcome	Time point							
	6 weeks (baseline to visit 4)		3 months (visit 4 to visit 5)		6 months (visit 5 to visit 6)		Total QALY gain	
	Sham group	Intervention group	Sham group	Intervention group	Sham group	Intervention group	Sham group	Intervention group
EQ-5D-5L-derived QALY gain								
n	2	4	2	4	2	4	2	4
Mean (SD)	0.075 (0.003)	0.059 (0.038)	0.068 (0.014)	0.069 (0.032)	0.167 (0.015)	0.155 (0.085)	0.309 (0.320)	0.283 (0.152)
Min.	0.073	0.007	0.058	0.023	0.156	0.028	0.290	0.060
Max.	0.076	0.094	0.077	0.094	0.178	0.200	0.330	0.370
SF-6D-derived QALY gain								
n	2	3[a]	2	3[a]	2	3[a]	2	3[a]
Mean (SD)	0.076 (0.017)	0.062 (0.007)	0.077 (0.023)	0.064 (0.014)	0.165 (0.036)	0.151 (0.037)	0.318 (0.076)	0.300 (0.044)
Min.	0.064	0.055	0.060	0.047	0.139	0.107	0.260	0.250
Max.	0.089	0.071	0.093	0.078	0.191	0.185	0.370	0.330

Max., maximum; min., minimum.
a One additional missing response because of missing data at baseline.

the framework for an economic analysis within a future trial. There are still questions to address but, even with the basic assessment carried out during this feasibility study, we have a good basis on which to take this development forward.

It seems clear that the study population are 'users' of health services, although there was little impact of the intervention on secondary care, with the main drivers of subsequent health resource use being associated with medications within primary care. Although the current resource use measure appears to capture relevant cost drivers, further work on developing a more precise measure (such as utilising routine secondary care data) to capture all relevant costs should be undertaken. Another possible area for consideration is the potential for imbalances between the groups at baseline. In a full randomised controlled trial, adjustment for baseline outcomes and other factors may be required. Although the feasibility study was designed to capture a UK NHS perspective only, the potential impact on patients, families and the wider society should be carefully considered in any future trial to capture the full picture.

The EQ-5D-5L and SF-6D data reflect the impact on health-related quality of life that the study participants experienced. Although formal conclusions cannot be drawn on the merits of either measure, the consensus from the team in light of this provisional investigation is that the EQ-5D-5L is likely to be the preferred measure, given its use in previous studies of back pain and its recommendation by UK decision-making bodies such as NICE[74,75] as the primary method of deriving QALYs. Further exploration of the findings from the feasibility study compared with the findings of other studies using these measure should be undertaken to fully rationalise the selection of appropriate outcomes to inform a future economic evaluation.

Study timelines

The start date of the study was delayed by 18 months (546 days), with 244 days taken to obtain NHS permission to recruit after obtaining a favourable research ethics opinion (*Figures 4* and *5*). A no-cost negotiated 1-month extension period was granted by the funder to allow for collection of follow-up data and delivery of the final report 45 days after collection of the final outcome data.

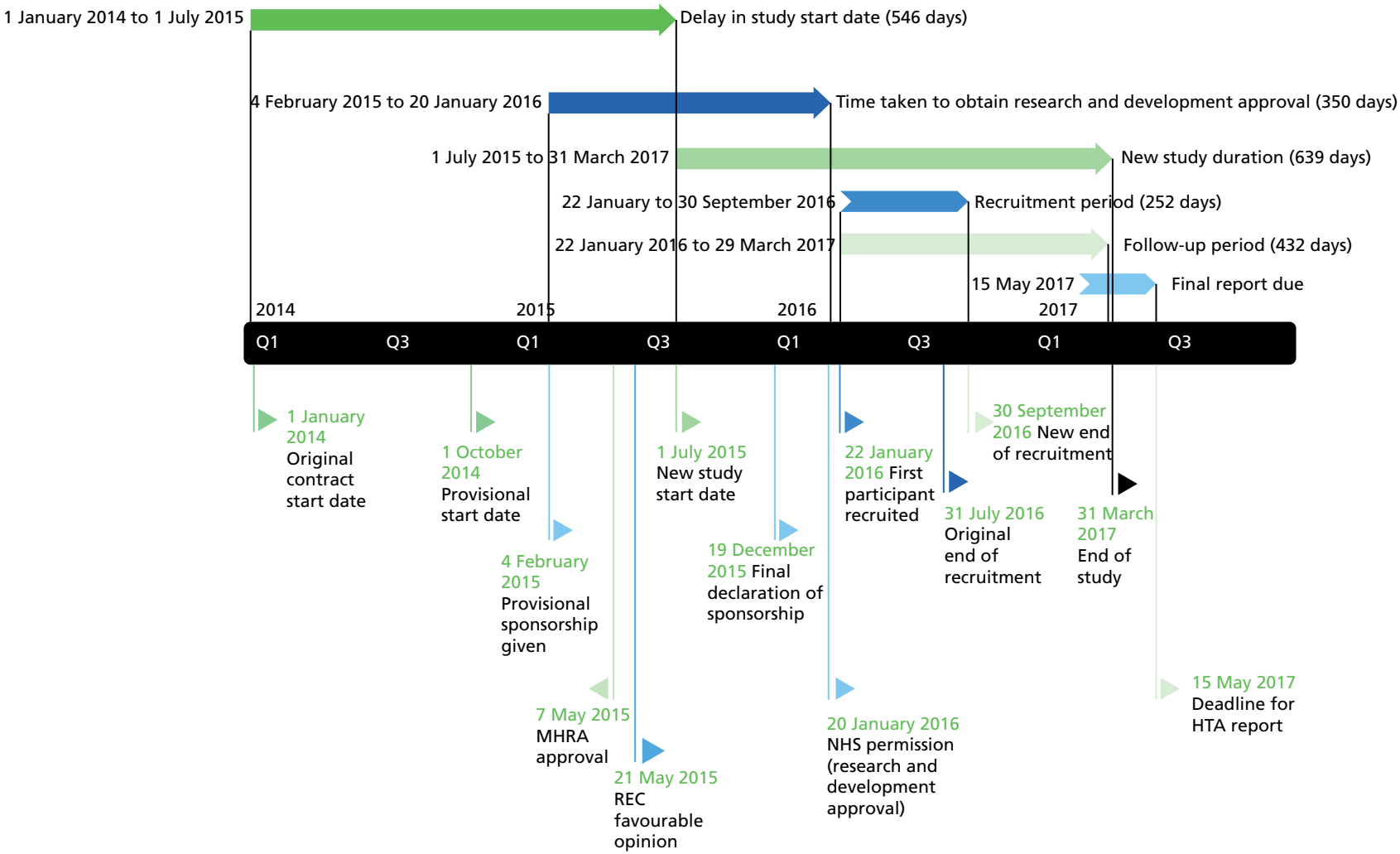

FIGURE 4 Study timelines and milestones. REC, Research Ethics Committee.

Month	−4	−3	−2	−1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	2015				2015								2016											2017			
	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May
Preparation Protocol refinement Statutory and regulatory requirements Prepare study documentation Recruitment and training of staff Promotion of project in clinics																											
Fieldwork Ongoing identification and recruitment of patients Outcome questionnaires – baseline Outcome questionnaires – 6 weeks after intervention Outcome questionnaires – 3 months after intervention Outcome questionnaires – 6 months after intervention																											
Intervention Diagnostic injections Facet-joint injections or sham procedure																											
Combined physical and psychological programme Training of physiotherapists Delivery of programme																											
Analysis and reporting Data coding, entry and cleaning Analysis Report writing Dissemination of results																											
Management Trial management group meetings Trial steering committee meetings	×						×					× ×				×					×	×			×		

FIGURE 5 Study Gantt chart.

Chapter 4 Discussion

Summary of findings

The overarching aim of the FACET feasibility study was to assess the feasibility of conducting a definitive study to evaluate the clinical effectiveness and cost-effectiveness of FJIs compared with a sham procedure in patients with non-specific LBP of > 3 months' duration.

We were unable to meet our feasibility objective of a recruitment target of 60 randomised LBP patients across three investigative sites. Instead, we were able to randomise only nine patients in one investigative site. However, we believe that we met our other pre-stated feasibility objectives within the constraints of this being a single-centre study with a small sample size: (1) we were able to select patients into the study using a joint clinical and diagnostic approach; (2) we have demonstrated successful standardisation of the methods of FJI and the sham procedure, using the Delphi method to generate consensus among interventional pain specialists in the UK; (3) we were able to carry out the sham procedure (periarticular injections with saline) in participants randomised to the control group; (4) the sham control study design was accepted by the clinicians involved in the study and was also deemed acceptable by patients; and (5) we were able to retain patients over the 6 months of follow-up.

The small number of participants recruited to the study and the feasibility design preclude us from drawing any conclusions on the clinical effectiveness or cost-effectiveness of intra-articular lumbar FJIs in the management of non-specific LBP. Additionally, although eight out of the nine patients randomised completed the study, the small sample size precludes any definitive conclusions being made about patient retention. However, the clinical procedures appeared to be safe and well tolerated, with no significant adverse events related to the steroid injection. Furthermore, we were able to successfully collect clinical and economic outcomes from the majority of the patients over the duration of the study.

Numerical differences between the groups were identified in the feasibility study (particularly with regard to increased medication costs in the intervention group) that warrant further attention, particularly given the inherent skewness in the data and the very small sample size.

The remainder of this chapter considers in more detail the findings of the feasibility study in terms of the detailed objectives, reviews the practical problems that were experienced and identifies the key learning outcomes for any definitive future trial in this area.

To assess the eligibility criteria and recruitment and retention of patients in the two treatment arms

Recruitment took place at only a single centre, largely because of the delay in study set-up and the decision by the funder to terminate the study early because of the lack of time available to open the other two sites. A number of reasons for this delay in set-up and time to first patient recruitment have been identified, including regulatory issues, staffing problems, specific recruitment challenges, factors affecting clinician and patient participation and the study population itself.

An unexpectedly high number of patients needed to be screened to identify eligible patients. The actual participant screening-to-recruitment ratio was 70 : 1 (628 : 9), which contrasts with the expected prestudy ratio of 17 : 1 (1000 : 60). The screening criteria and recruitment rates were discussed at each TMG meeting and it was perceived by some members of the group that the inclusion and exclusion criteria may have excluded potentially eligible patients, such as those aged > 70 years who would otherwise have been suitable.

Over the period of the trial, five participants (31%) dropped out of the study after giving consent but before receiving the diagnostic test (see *Figure 3*). This compared with our expected level of attrition. We were able to collect study data from participants at baseline and at the various follow-up points. The level of outcome completion varied across outcomes, with 11 out of 16 participants who completed the baseline questionnaire returning incomplete data sets, ranging from entire questionnaire visits being omitted to one section of a single questionnaire being missing or spoiled (illegible). Missing and incomplete outcome data are detailed further in *Appendix 11*. Manual double data entry, considered to be the gold standard for data transfer,[76] was used by two independent researchers and ensured the high quality of data entry onto the electronic database.

An apparently high level of participant retention was seen in this trial, with an average attrition rate of 11%, that is, only one patient out of nine randomised failed to complete the final set of questionnaires at 6 months. This compares favourably with the expected attrition rate of 20% defined in the protocol. However, given the small sample size this estimate of attrition was very imprecise, with a 95% CI of 0.2% to 48%.

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

A Delphi exercise was undertaken with interventional pain physicians in the UK to agree on the methods for FJI and the sham procedure (see *Appendix 6*). The two treatments arms (FJIs and the sham procedure) can therefore be considered to be feasible and acceptable by pain clinicians. Furthermore, all six pain consultants at Barts Health NHS Trust screened and recruited participants to the study. Strong support was also given from the surgeons and research physiotherapists involved in screening patients from the spinal orthopaedic clinics at the centres involved in this study.

Of the 34 patients who met the eligibility criteria but who declined to take part in the study, none cited the study design as the reason for not wishing to take part.

To assess the feasibility of the proposed definitive study design

We believe that this study did allow us to demonstrate the feasibility of the study design to inform a definitive study. We were able to develop an appropriate active injection technique (intra-articular lumbar FJI) and sham procedure. No patients refused participation on the grounds of randomisation to an active or a sham procedure. We were able to maintain blinding of patients as only one of the eight participants who completed the study correctly guessed their allocation group. The outcome assessors correctly guessed four out of nine allocation groups over the period of the trial.

A key uncertainty going into this study was the feasibility of delivering a usual care CPP programme to both study arms. The 2009 NICE guidelines for the early management of persistent non-specific LBP (CG88)[7] prescribed around 100 hours of a CPP programme over a maximum of 8 weeks for those who have already received at least one less-intensive treatment such as an exercise programme, manual therapy or acupuncture and who have 'high disability and/or significant psychological distress'.[7] However, following careful discussion by the TMG and a review of the current evidence we instead decided to base delivery of our CPP programme in this trial on the BeST trial,[44] which recommended six sessions of group-based therapy (up to 10 participants) of 90 minutes each. The study's lead physiotherapist (SP) trained all of the study physiotherapists across the three sites to deliver the CPP programme and all received a certificate of training.

Three CPP programmes were consistently delivered at Barts Health NHS Trust, albeit to small groups of participants (one to three participants per group); the BeST trial found that a group size of six to 10 participants was clinically effective and cost-effective and popular in clinical practice in that it allows for group discussion and problem-solving.[44] Six out of nine (67%) participants successfully completed the CPP programme, defined in the protocol as having attended at least four out of the six sessions. The other three participants failed to meet this protocol definition of CPP programme attendance because of extenuating circumstances (illness, undisclosed personal reasons and travel abroad).

Since our original trial proposal, the NICE guidelines (CG88)[7] on the management of LBP have been updated. The current 2016 NG59[10] draws on evidence from the BeST trial[44] and no longer specifies the length or duration of the CPP programme, instead stating:

> *Consider a combined physical and psychological programme, incorporating a cognitive behavioural approach (preferably in a group context that takes into account a person's specific needs and capabilities), for people with persistent LBP or sciatica:*
>
> - *when they have significant psychosocial obstacles to recovery (for example, avoiding normal activities based on inappropriate beliefs about their condition) or*
> - *when previous treatments have not been effective.*
>
> *© NICE 2017. Reproduced with permission from NG59.* Low Back Pain And Sciatica in Over 16s: Assessment and Management. *Available from www.nice.org.uk/guidance/ng59. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

Thus, we believe that CPP programme delivery in our trial was well aligned with the latest NICE guidance.

To estimate outcome standard deviations to inform the power calculation for a definitive study

We have reported the SDs for all proposed clinical and economic outcomes at baseline and follow-up. However, given the small final sample size realised we express caution in using these SDs to inform the sample size calculation for a future definitive study. Following their simulation analysis, Teare *et al.*[77] recommended that an external pilot study has at least 70 measured subjects (35 per group) when estimating the SD for a continuous outcome. Similarly, the sample size in this study was also inadequate to provide a sufficiently precise estimate of attrition. Probably the only parameter for a future definitive study that this study was able to estimate with precision was the screening/recruitment rate.

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

Given the failure to meet the study recruitment target and the small number of patients recruited from one centre, the study team deemed it inappropriate to present a finalised protocol for a definitive study on the basis of this feasibility study.

Issues encountered and how they were resolved

This feasibility study encountered system-level barriers but no significant delays in obtaining research ethics or MHRA approval.

Regulatory issues

The projected recruitment period for this feasibility study occurred during a time of change within research governance, which in turn led to significant delays in regulatory approvals being granted (see *Figure 4*). Delays were experienced in obtaining HRA approval and system errors led to further delays in obtaining NIHR portfolio adoption and NHS permission. The large numbers of collaborating centres involved led to delays in contracts being signed. The study team also noted the length of time taken for any issues to be addressed at a local level.

Staffing issues

The changes in the study timeline meant that key members of the co-applicant team were unable to commit to the study: the Chief Investigator (Richard Langford) and lead physiotherapist (Paul Watson) retired from clinical practice, the trial co-ordinator was replaced and others had conflicting interests and

priorities. A high staff turnover rate within the local research governance team, including several changes of trial pharmacist and a change of trial monitor, resulted in some duplication of work, in part because of inadequate handovers. Substantial amendments to the protocol were made to reflect staff turnover and also on the request of the new trial monitor, resulting in further recruitment delays.

Recruitment challenges

The low recruitment rate from the pain clinics alone led to protocol amendments to allow for screening at and recruitment from physiotherapy-based musculoskeletal clinics and spinal orthopaedic clinics (see *Appendix 10*). A recruitment drive was put into place within the last 2 months of the recruitment phase, led by a newly appointed trial mentor, using strategies to increase the number of patients eligible for screening within the limitations of the study protocol. A no-cost recruitment extension period was also granted by the funder.

However, it can be seen in *Appendix 12* that, although the number of patients screened increased as a result, the number of participants recruited did not. A future multicentre trial may wish to consider the early addition of a recruitment co-ordinator to the core study team, to closely monitor the recruitment rate at each site and implement a priori contingency plans with the sites' Principal Investigators should the recruitment rate fall below the predicted rate. Based on our experience, we would advise the appointment of a study mentor (who is an experienced triallist) to review the recruitment rate at each site and to implement strategies to improve this. This may include the appointment of additional research assistants to screen for suitable patients from a wider range of clinics (e.g. associated community pain clinics and spinal orthopaedic clinics) and from GP referral letters. Protocol amendments were made to reflect these changes (see *Appendix 10*). McDonald *et al.*[78] demonstrated that recruitment strategies can change as a result of pilot or feasibility phases of a study.

We conclude, however, that the target population for the study was not always being referred to the hospital pain and spinal orthopaedic clinics. We were unable to explore this further in the feasibility study but would propose this as an area for future exploration in terms of the definitive trial design. The recruitment estimates used for the feasibility study were based on the clinical experience of the investigators and a retrospective audit of procedures carried out at each of the three centres. It was initially believed that five patients would be recruited from the pain clinics at Barts Health NHS Trust each week, with three patients recruited each from Basildon and Thurrock University Hospitals NHS Foundation Trust in Basildon and the Walton Centre NHS Foundation Trust in Liverpool. A comparison of the actual with the expected flow of participants through the study is illustrated in *Appendix 13*. Although the actual number of participants recruited in the study was lower than expected, it is hoped that this work will guide future research in this area by providing more realistic and up-to-date data and by highlighting the areas in the recruitment pathway that pose the greatest challenges to recruitment.

Clinician and patient participation

In their systematic review, Prescott *et al.*[79] identified a number of factors that may affect clinician participation in a study. These include time constraints and a lack of staff and training. Clinicians may also have competing priorities during the study recruitment period, for example from involvement in other trials. This feasibility study recruited from a busy NHS trust in which clinicians have time pressures from usual clinical practice in the pain clinics as well as ongoing management duties. All of the study interventions and pain consultant clinic appointments were scheduled alongside routine NHS appointments.

At the time of writing, the pain clinics at St Bartholomew's Hospital at Barts Health NHS Trust accept referrals via the NHS e-Referral Service (formerly Choose and Book) from a wide catchment area across the country in addition to its local area in East London. Travel and travel costs can therefore be substantial for some patients, some of whom have limited mobility because of their pain condition and may even require hospital transport. Travel costs and the time taken to attend for appointments may therefore be a factor contributing towards non-participation. Study participants may also have other commitments that preclude their attendance at study visits, such as full- or part-time employment or caring for young children.

Five out of sixteen patients who consented to take part in the study dropped out before treatment for reasons that remain speculative. Of the nine patients who took part, six completed at least four sessions of the CPP programme. It may be possible to improve participant retention in a definitive trial by including more detailed information on the CPP programme in the participant information sheet and by involving the public in its preparation to make the information easier to understand.

Study population

The study population presenting to pain clinics at Barts Health NHS Trust was noted to have complex pain needs, often with co-existing radicular pain or chronic widespread pain conditions, in addition to suffering from psychological distress. Although approximately 1050 new patients are referred and seen annually in the pain clinics at St Bartholomew's Hospital, it was clear that many of these 'new' patients were not new to the pain services, having had previous spinal injections or surgery, for example. None of the patients screened in the spinal orthopaedic clinics were eligible to take part in the study for these reasons and many of the referrals also had radicular pain, indicative of a lumbar disc pathology.

No patients were recruited from the Tower Hamlets Persistent Pain Services at Mile End Hospital. The London Borough of Tower Hamlets has a diverse ethnic population and experiences widespread deprivation and low average health deprivation scores, with a high rate of population mobility.[80] Although an inability to speak English was not an exclusion criterion for the study, translation and patient advocacy services for non-NHS study-related visits were not funded for. Language barriers have been highlighted by previous researchers as being a negative influence on recruitment, with altruism noted to be an important factor in deciding to take part.[81] We believe that this could be an area for further investigation in a future trial, to make research more accessible to diverse local populations.

The highest participant screening-to-recruitment ratio was seen in the community pain clinic at Essex Lodge GP surgery, which has strong, established links to primary care and is located at the same site as the GP surgery. Patients were thought to be referred to this pain service by the local GPs earlier in their pain trajectory than in other pain clinics in this study. This feasibility study has demonstrated the need for more primary care involvement at all stages of the study, from protocol design and patient screening and recruitment to dissemination of the results. A need for improved referral pathways between the pain services and some primary care providers has been identified.

Strengths and limitations

Many of the key uncertainties involved in undertaking a definitive study were addressed in this feasibility study.

Major strengths of the study were the Delphi exercise, which was undertaken to obtain a consensus on the procedural techniques, and that the interventional procedures themselves were shown to be safe and reproducible. Furthermore, the positive response in nine out of 11 participants (82%, 95% CI 48% to 98%) following the single diagnostic lumbar facet medial branch nerve block indicates some accuracy of the assessment performed by the clinical team in determining pain of lumbar facet-joint origin based on history and clinical examination alone. However, the results are imprecise because of the small sample size. We have shown that the CPP programme is deliverable at a single recruiting centre and that it was possible to train the study physiotherapists to deliver the programme at each of the three planned recruitment centres. We were able to retain most of the recruited participants for the duration of the study.

Embedding a health economics assessment into the feasibility study allowed us to obtain important insights that can be used to develop the framework for an economic analysis within a future trial. Although the feasibility study was not primarily designed to act as a formal microcosting exercise, we have endeavoured to capture all salient aspects of the patient pathway relevant to the intervention using a triangulation of data sources, including trial documentation and structured questions to the clinical experts and discussion

with the trial team, with validation of any assumptions made throughout the costing procedure. We have also been transparent in the costing methods employed, as detailed in *Appendix 9*. A recognised limitation of our analysis is that the resource use questionnaire was not sufficiently comprehensive to capture all health-care resource use nor did we investigate the potential for other approaches (including capturing routine data in a systematic manner). In future feasibility studies we suggest that a worthwhile endeavour would be to undertake a more 'bottom-up' exercise of costing, subject to trial resources being available to do so. We therefore recommend that, in a future trial, the current measure is tested and challenged against existing measures [e.g. search of the DIRUM (Database of Instruments for Resource Use Measurement);[82] see *Table 29* in *Appendix 9*], including investigating ways that data can be collated [such as using routine sources such as Hospital Episode Statistics (HES) and/or utilising patient diaries to collect data, e.g. related to primary care contacts and medication use].

The main weakness of the study was the failure to achieve our expected recruitment targets and the consequent early closure by the funder. There were substantial system-level barriers that the study team were unable to control (such as delays in obtaining HRA approval and changes in key study personnel), which led to long delays in obtaining research governance approvals, and permission to recruit was granted at only a single site.

It became clear early in the recruitment phase that many patients presenting to the pain clinics with LBP of > 3 months' duration were not suitable for the study and that patients screened in the spinal orthopaedic clinics also did not meet the eligibility criteria. Despite employing additional strategies in the final stages of recruitment, we can conclude that the patient population presenting to these hospital-based specialist clinics was generally not suitable because of the complexity of their pain problems and that we may have had better success in recruiting from primary care-based services.

We would advise caution in extrapolating the results of this study as the study took place at a single centre in a secondary care setting. Patients presenting to primary care may additionally have lower levels of functional disability, despite high levels of pain intensity.

The feasibility study resulted in a number of suggestions for refinements to data collection, including resource use. One of the key balances has to be the development of a measure (method) of capturing resource use that is sufficiently comprehensive and accurate enough to capture important and relevant changes while not overburdening the trial in capturing extensive and irrelevant drivers of costs. The derived measure was driven primarily by clinical expertise; however, this must of course be balanced with the needs of the health economist in terms of having data of sufficient quality to undertake a comprehensive and transparent costing exercise. *Appendix 14* presents recommendations from reflecting on the current measure of resource capture.

Because of the trial limitations, we were able to present only a descriptive profile using the EQ-5D-5L and SF-6D to determine utilities; thus, any interpretation of our findings should be appropriately tentative. The choice of which measure to use should also be considered further, given the potential for different numbers of QALYs to be generated by different measures and the subsequent impact on calculations of cost-effectiveness.[73]

Implications for a future definitive study

Neither of the research teams funded by the HTA programme to investigate the feasibility of carrying out a definitive study to assess the use of lumbar FJIs for persistent non-specific LBP met the target recruitment rate. Professor Underwood's team concluded that a definitive study is indeed feasible, but that recruitment from the pain clinics alone was insufficient.[83] Both teams experienced significant delays in study set-up.

Any future definitive trial must consider patient and public involvement at all stages of the research cycle, including in the design and running of the trial and representation on the TMG.

Low back pain and sciatica were selected by the Trauma Programme of Care Board as their Pathfinder Project; these projects were established by NHS England in 2013 to set up clear 'end-to-end' generic pathways from primary care into specialised services as required, enabling collaborative commissioning and incorporation of the latest evidence into the pathways. The National Low Back and Radicular Pain Pathway 2017[84] was updated following the publication of NG59[10] and includes all of NICE's recommendations. Improved co-ordination and communication with GP practices is necessary for any future collaborative work and we envisage working alongside the Pathfinder Project (in which spinal injections are not recommended) to recruit patients from primary care with high levels of functional disability who may benefit from such an intervention and rehabilitation at an earlier stage. One finding from the feasibility study was the long duration of pain awareness among the study participants, which warrants further investigation as this may reflect the time taken for patients to be referred to specialist clinics.

Based on our findings, we propose three research recommendations. First, we would agree with the Underwood team that a definitive study is potentially feasible, with adjustments made to the target population and increased primary care involvement, to enable patients to be screened earlier in their pain trajectory. Second, a definitive study will need to draw on lessons learned from both research teams (such as the recruitment enhancement strategies) and could involve a future collaboration between the two research groups, combining the successful elements of the feasibility studies. The updated NICE guidelines[10] recommended radiofrequency denervation of the lumbar facet-joint medial branch nerves in patients with LBP that have not responded to less invasive treatments, following a positive diagnostic block; this is in contrast to a recent Cochrane review that has not recommended its use.[85] There is, however, new evidence from a large multicentre Dutch trial that radiofrequency denervation offers no clinical benefit compared with a sham procedure.[86] Third, as both intra-articular injections and radiofrequency denervation are widely used in the UK, we contend that there remains a need for future definitive studies to assess the clinical effectiveness and cost-effectiveness of both of these procedures in the management of persistent LBP.

Chapter 5 Conclusions

A successful trial can be defined as one that achieves success in recruitment and is able to answer the research questions. Although we have successfully demonstrated our ability to develop a robust study protocol and deliver the intended interventions, and addressed many of the feasibility objectives, the failure to achieve the target recruitment rate remains a key finding of this study. However, there are lessons to be learned here that can be used to inform and improve patient recruitment for a future definitive study. To optimise recruitment for a definitive study we would contend that any future studies in this area should involve stronger collaborations with primary care physicians and musculoskeletal physiotherapy teams to identify and recruit potential participants earlier in their pain trajectory, with the aim of making these procedures more accessible to these patients who would not otherwise have been referred on for specialist services.

Acknowledgements

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Contributions of authors

Saowarat Snidvongs (Consultant in Anaesthesia and Pain Medicine) was the Principal Investigator at Barts Health NHS Trust, drafted the manuscript and carried out the diagnostic injections, facet-joint injections and sham procedure.

Rod S Taylor (Professor of Health Services Research, Director of the Exeter Clinical Trials Unit and NIHR Senior Investigator) was the study statistician and a co-applicant, contributed to the protocol design and development, drafted the statistical analysis plan, undertook statistical analyses for the study and contributed to writing of the manuscript.

Alia Ahmad (Research Assistant) was the trial co-ordinator and was responsible for facilitating and co-ordinating the study by maintaining trial activities and paperwork according to good clinical practice.

Simon Thomson (Consultant in Anaesthesia and Pain Medicine) was the Principal Investigator at Basildon and Thurrock University Hospitals NHS Foundation Trust and a co-applicant, contributed to the protocol design and development and reviewed the final manuscript.

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Angela Farr (Health Economist and Data Analyst) contributed to the writing of the health economics analysis plan, undertook the health economics analysis, drafted the health economics results and detailed costing methodology and provided feedback on all aspects of the health economics sections and the final draft of the manuscript.

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Conferences

The study protocol was presented as a poster at the International Association for the Study of Pain's 16th World Congress on Pain in Yokohama, Japan, in September 2016. The preliminary results were presented as a poster at the British Pain Society's 50th Anniversary Annual Scientific Meeting in Birmingham, UK, in May 2017. The full study was presented as a poster at the European Pain Federation's 10th Congress in Copenhagen, Denmark, in September 2017; the critical appraisal of systematic reviews was also presented as a poster at the same congress. The study has been accepted as a poster presentation at the Society for Back Pain Research in Northampton, UK, in November 2017.

Thesis in preparation

The FACET feasibility study will form the basis of Dr Snidvongs's Doctor of Medicine thesis entitled 'Lumbar facet-joint injections for the management of chronic low back pain'. This will be submitted to the University of Exeter in 2017.

Data sharing statement

We shall make data available to the scientific community with as few restrictions as feasible while retaining exclusive use until the publication of major outputs. Requests for the data should be made to the corresponding author (Dr Saowarat Snidvongs).

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Appendix 1 Search strategies for the literature search of systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar facet-joint injections for chronic low back pain

MEDLINE

Date range searched: 1966 to 6 February 2017.

#	Search term	Results
1	exp *LOW BACK PAIN/	13,733
2	("low back pain").ti,ab	21,120
3	exp *ZYGAPOPHYSEAL JOINT/	961
4	("facet joint").ti,ab	2227
5	exp *CHRONIC PAIN/ OR exp *PAIN/	218,391
6	(lumbar OR paravertebral).ti,ab	91,494
7	exp *LUMBAR VERTEBRAE/	26,956
8	1 OR 2	24,954
9	3 OR 4	2683
10	6 OR 7	98,948
11	5 AND 10	9560
12	8 OR 9 OR 10 OR 11	117,090
13	exp *INJECTIONS, INTRA-ARTICULAR/	809
14	("intra articular*").ti,ab	12,196
15	(facet ADJ2 injection).ti,ab	143
16	(facet ADJ2 joint).ti,ab	2299
17	exp *FLUOROSCOPY/	5060
18	(fluoroscop*).ti,ab	21,046
19	exp *THERAPEUTICS/	2,895,415
20	(therap*).ti,ab	2,169,176
21	("percutaneous spinal").ti,ab	94
22	13 OR 14	12,630
23	15 AND 16	120
24	17 OR 18	23,098
25	19 OR 20	4,590,592
26	exp *INJECTIONS/	20,026
27	(injection*).ti,ab	496,795
28	26 OR 27	505,646
29	21 AND 28	7
30	22 OR 23 OR 24 OR 25 OR 29	4,610,334

#	Search term	Results
31	12 AND 30	49,755
32	("systematic review*").ti,ab	94,141
33	31 AND 32	1138
34	("meta analysis").ti,ab	88,442
35	31 AND 34	521
36	("control* trial*" OR RCT).ti,ab	13,597
37	31 AND 36	179
38	33 OR 35 OR 37	1504
39	(facet).ti,ab	10,869
40	32 AND 39	123

EMBASE

Date range searched: 1966 to 6 February 2017.

#	Search term	Results
1	exp *LOW BACK PAIN/	23,697
2	("low back pain").ti,ab	28,245
3	exp *ZYGAPOPHYSEAL JOINT/	509
4	("facet joint").ti,ab	2999
5	exp *CHRONIC PAIN/ OR exp *PAIN/	386,200
6	(lumbar OR paravertebral).ti,ab	123,427
7	exp *LUMBAR VERTEBRAE/	7855
8	1 OR 2	35,444
9	3 OR 4	3251
10	6 OR 7	125,759
11	5 AND 10	16,010
12	8 OR 9 OR 10 OR 11	151,862
13	exp *INJECTIONS, INTRA-ARTICULAR/	1884
14	("intra articular*").ti,ab	15,071
15	(facet ADJ2 injection).ti,ab	193
16	(facet ADJ2 joint).ti,ab	3056
17	exp *FLUOROSCOPY/	6811
18	(fluoroscop*).ti,ab	34,353
19	exp *THERAPEUTICS/	3,002,010
20	(therap*).ti,ab	3,111,511
21	("percutaneous spinal").ti,ab	138
22	13 OR 14	16,232
23	15 AND 16	165
24	17 OR 18	35,845
25	19 OR 20	5,235,530

#	Search term	Results
26	exp *INJECTIONS/	33,580
27	(injection*).ti,ab	635,413
28	26 OR 27	639,110
29	21 AND 28	11
30	22 OR 23 OR 24 OR 25 OR 29	5,270,243
31	12 AND 30	38,627
32	("systematic review*").ti,ab	118,882
33	31 AND 32	867
34	("meta analysis").ti,ab	117,968
35	31 AND 34	428
36	("control* trial*" OR RCT).ti,ab	231,428
37	31 AND 36	2362
38	33 OR 35 OR 37	2906
39	(facet).ti,ab	12,624
40	32 AND 39	149

Cochrane Central Register of Controlled Trials

Date range searched: 1966 to 6 February 2017.

Search strategy

#1 MeSH descriptor: [Back Pain] explode all trees

#2 back near pain

#3 dorsalgia

#4 back disorder*

#5 backache

#6 MeSH descriptor: [Low Back Pain] explode all trees

#7 (lumbar next pain)

#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)

#9 MeSH descriptor: [Zygapophyseal Joint] explode all trees

#10 facet near joints

#11 zygapophysial*

#12 (#9 or #10 or #11)

#13 (#8 and #12)

Appendix 2 Systematic review articles on therapeutic lumbar facet-joint injections identified from the database searches

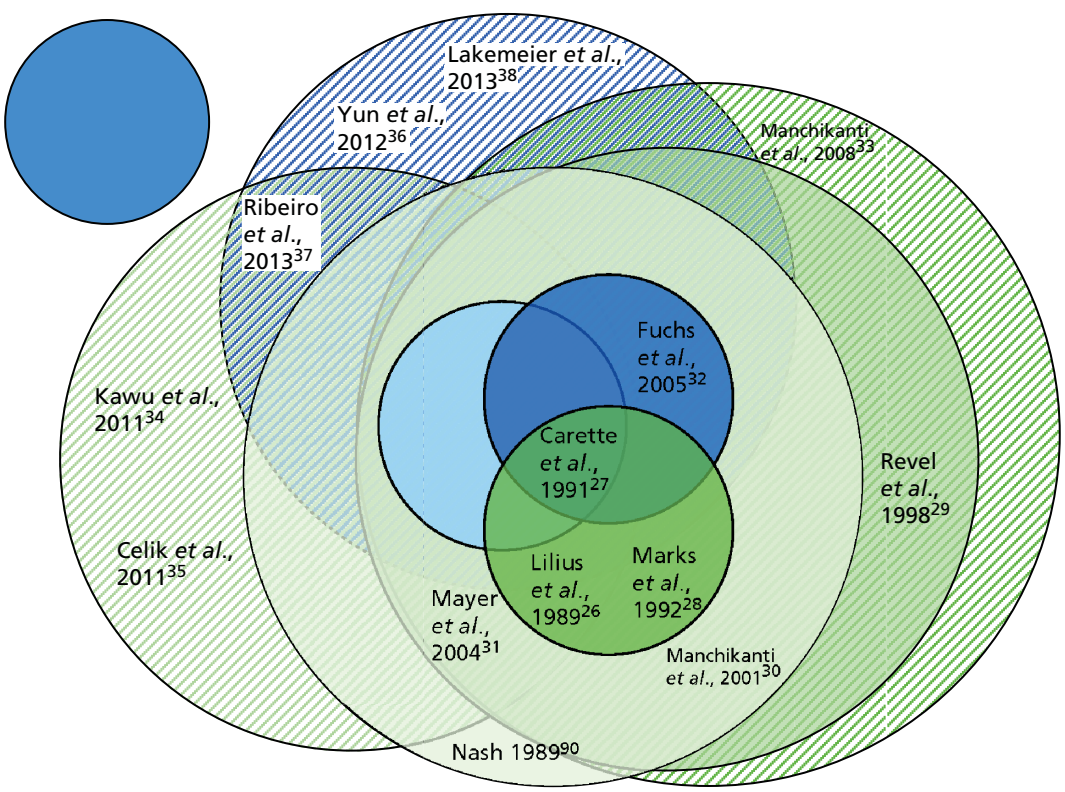
Source	First author, year of publication													
	Slipman *et al.*, 2003[14]	Boswell *et al.*, 2005[87]	Boswell *et al.*, 2007[15]	Staal *et al.*, 2008[16]	Staal *et al.*, 2009[88]	Datta *et al.*, 2009[17]	Chou *et al.*, 2009[18]	Henschke *et al.*, 2010[19]	Falco *et al.*, 2012[20]	Manchikanti *et al.*, 2015[21]	Boswell *et al.*, 2015[89]	Manchikanti *et al.*, 2015[22]	Vekaria *et al.*, 2016[23]	Manchikanti *et al.*, 2016[24]
MEDLINE														
EMBASE														
CENTRAL														
Other sources														
Reasons for exclusion if applicable		Published update			Duplicate publication						Intervention not of interest			

Appendix 3 Assessment of Multiple Systematic Reviews (AMSTAR) checklist scores for the included systematic reviews

First author, year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	AMSTAR score[a]
Slipman, 2003[14]	CA	CA	N	N	Y	Y	Y	Y	CA	N	CA	4
Boswell, 2007[15]	CA	CA	Y	CA	Y	Y	Y	Y	CA	N	CA	5
Staal, 2008[16]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	CA	8
Datta, 2009[17]	CA	CA	Y	CA	Y	NA	NA	NA	NA	N	CA	2
Chou, 2009[18]	CA	Y	Y	Y	Y	N	Y	Y	N	N	CA	6
Henschke, 2010[19]	CA	CA	N	N	Y	Y	Y	Y	Y	Y	N	6
Falco, 2012[20]	CA	Y	Y	CA	Y	Y	Y	Y	Y	N	CA	7
Manchikanti, 2015[21]	CA	Y	Y	CA	Y	Y	Y	Y	Y	N	N	7
Manchikanti, 2015[22]	CA	Y	Y	CA	N	Y	Y	Y	Y	N	CA	6
Vekaria, 2016[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CA	10
Manchikanti, 2016[24]	CA	Y	Y	CA	N	Y	Y	Y	N	N	CA	5

CA, can't answer; N, no; NA, not applicable; Y, yes.
a Maximum score 11.

Appendix 4 Venn diagram to illustrate the randomised controlled trials included in each systematic review



Systematic review paper	
Slipman *et al.*, 2003[13]	
Boswell *et al.*, 2007[14] Falco *et al.*, 2012[19]	
Staal *et al.*, 2008[15]	
Datta *et al.*, 2009[16]	
Chou *et al.*, 2009[17]	
Henschke *et al.*, 2010[18]	
Manchikanti *et al.*, 2015[21] Manchikanti *et al.*, 2016[23]	
Manchikanti *et al.*, 2015[20]	
Vekaria *et al.*, 2016[22]	

Appendix 5 Participant information sheet

PARTICIPANT INFORMATION SHEET

Title of study: 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

Principal Investigator: Dr Saowarat Snidvongs

REC reference: 15/LO/0500

EudraCT number: 2014-003187-20

Version 6.1 25th August 2016

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and healthcare professionals if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Low back pain is common in adults, and may lead to chronic disability. Lumbar facet-joints are small, paired joints in the low back that provide stability, integrity and flexibility of movement to the spine. Diseased facet-joints may cause persistent low back pain.

Although the pain may be treated with targeted facet-joint injections, there is currently no high quality or definitive clinical evidence to support their use. The National Institute for Health and Care Excellence (NICE) therefore do not currently support the use of lumbar facet-joint injections in treating low back pain due to the lack of high quality evidence.

This is a preliminary study to see whether it is feasible to conduct a larger definitive trial to assess lumbar facet-joint injections (a needle is inserted into the facet-joint and steroid injected) by comparing it to a dummy or 'sham' procedure (a needle is inserted near the facet-joint but no therapeutic substance injected).

The purpose of a feasibility study is to help researchers decide whether the intervention (lumbar facet-joint injections for low back pain) is appropriate for further testing in a larger definitive trial.

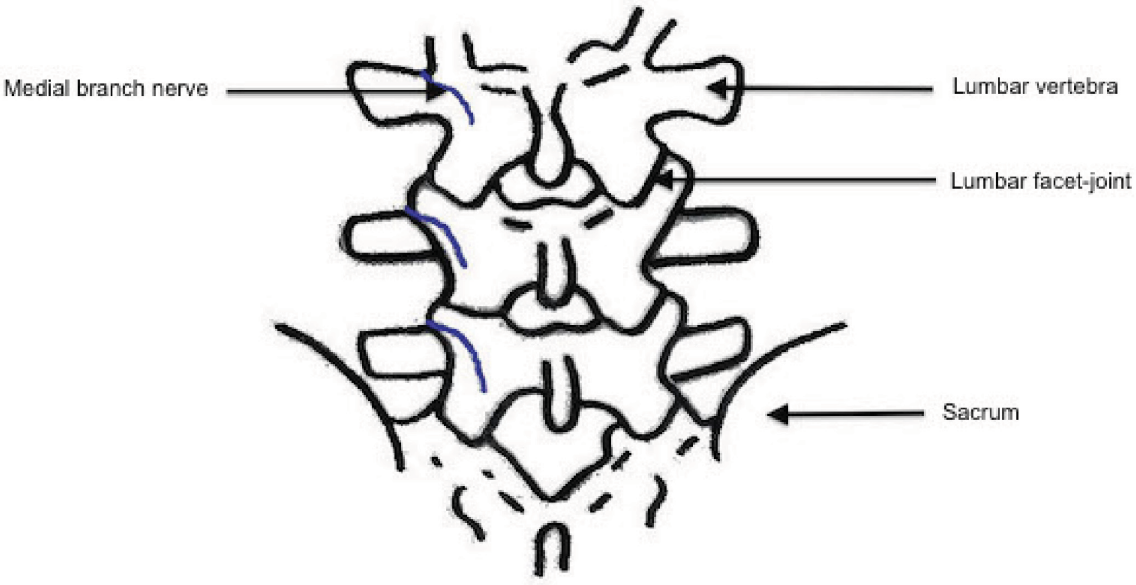


Diagram of the lower part of the vertebral column or backbone

Why have I been chosen?

You have been chosen because you have been referred to the pain clinic with low back pain of greater than three months' duration that may be of facet-joint origin. The pain has not improved despite best non-invasive care as recommended by NICE (pain education, and one or more of the following: physical education programme, acupuncture, and manual therapy).

Do I have to take part?

The decision to participate in this study is entirely up to you. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form; you are still free to change your mind and may withdraw from the study at any time and without

giving a reason. A decision to withdraw from the study at any time will not affect the standard of care that you receive now or in the future.

If you do decide to withdraw from the study, we will retain any data obtained prior to withdrawal. We will not collect any further data from you in relation to this study. You will be followed-up in the pain clinic as part of usual NHS practice.

What will happen to me if I take part?

You will first receive an appointment to have a diagnostic test for lumbar facet-joint disease. This is an injection of local anaesthetic into your low back to block the painful nerve supply to the facet-joints (medial branch nerve block). Depending on your response, you may receive a second appointment to return for either the facet-joint injections or a sham procedure. You will have an equal chance of being in either group.

The sham procedure is a 'dummy' injection near to, but not in, the facet-joint with a saline solution (no drug action). This is a necessary part of the study design, as it will enable the two procedures to be compared. You will not know whether you have been given facet-joint injections or a sham procedure, as this has been shown to be one of the best ways we have for knowing what the intervention (lumbar facet-joint injections for low back pain) really does.

An expert, who is a Consultant in Pain Medicine and the Principal Investigator at your site, will carry out all the injections. The procedures will take place in a dedicated sterile environment, such as an operating theatre in a hospital day surgery unit. You will lie on your front awake for the duration of the injections, which usually take no more than 20 to 30 minutes to complete. You will go home on the same day.

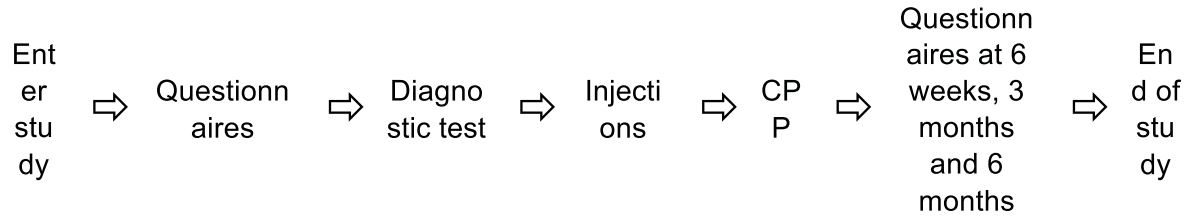
You will be invited to attend six sessions of a combined physical and psychological programme (CPP) after your injections. These will be delivered to you in small groups by a trained physiotherapist and each session will last for 90 minutes. The CPP has been recommended by NICE as a strategy to reduce pain and its impact on day-to-day life, even if the pain cannot be cured completely.

You will be required to attend six separate hospital or clinic appointments, in addition to the CPP. The first three appointments are with a Consultant in Pain Medicine and are part of routine clinical practice (initial consultation, diagnostic test, and facet-joint injections or sham procedure).

There are three follow-up visits with a research nurse after your injections, which will take place in a research clinic to complete a set of questionnaires relating to your pain and

health-related quality of life. You will complete four sets of questionnaires in total (before the injections, and 6 weeks, 3 months and 6 months after the injections).

The study will end when you complete your final set of questionnaires, six months after the injections.



What are the side effects of taking part?

The diagnostic injections and facet-joint injections are commonly performed and considered safe. The procedures may be uncomfortable but are not considered painful, and are generally well tolerated with you being awake. You may experience a brief stinging sensation when we numb your skin with a local anaesthetic. The same applies for the sham procedure group.

Minor side effects from the diagnostic injections and facet-joint injections are not uncommon and include bruising at the site of injection. Other complications include technical failure (we are unable to perform the procedure), failure to relieve pain, injury to nerves, and infection. Major complications are extremely rare.

Ionising radiation in the form of x-rays will be used in both groups – this is necessary to allow the needles to safely enter the correct space in your back. Exposure to ionising radiation increases the risk of incurring cancer in later life. The radiation dose received has been assessed by a medical physics expert and is considered to be of very low risk, comparable to about 2 months of background (environmental) radiation exposure.

What are the possible disadvantages of taking part?

There are no disadvantages in taking part in this study although it may take some time (up to an hour) to complete the questionnaires. If you are in the sham group, you are not expected to obtain any pain relief from your procedure but you will be followed-up in the pain clinic by a Consultant in Pain Medicine and offered further treatment to manage your pain as required, including facet-joint injections.

What are the possible benefits of taking part?

If you are in the treatment group and receive lumbar facet-joint injections, you may experience symptomatic relief of your low back pain. If you are in the sham group, there may be no direct benefit to you but we anticipate that the results of the study could benefit future patients with low back pain, by increasing their treatment options.

What if more information becomes available?

Sometimes during the course of a research study, new information becomes available about the treatment or medicine being studied. We will inform you of any new developments should this occur.

What happens if there is a problem?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. If you wish to complain formally, you can do this through the NHS complaints procedure. Details of this can be obtained from the Patient Advice and Liaison Service [insert local details here].

Will my taking part be kept confidential?

Your confidentiality will be safeguarded during and after the study, with data handling, processing and storage carried out according to the Data Protection Act 1998. Any individual data will be anonymised and given a research code, and all paper data will be stored in a locked cabinet within a locked office in the Pain and Anaesthesia Research Centre at Barts Health NHS Trust in London. Electronic data will be stored on a password-protected computer accessed only by members of the research team. The data generated by the study will be entered by the research team onto an electronic database developed by the Peninsula Clinical Trials Unit, and will be analysed confidentiality at the University of Exeter by Professor Rod Taylor the study statistician.

Regulatory authorities and the study Sponsor may also look at the study data, to ensure that the study is being carried out correctly.

Involvement of your general practitioner

With your permission, your GP will be informed that you are taking part in this study. We may contact your GP prior to contacting you during the study to make sure your personal circumstances have not changed since our last contact.

What will happen to the results of the research study?

The results of the study will be entered onto a database by the research team at the Pain and Anaesthesia Research Centre at Barts Health NHS Trust, and analysed with statistical advice from the University of Exeter.

The results will be published in a report upon completion of the study, and may be made available to you on request. It is anticipated that the study will run for 21 months. You will not be identified in any report or publication.

Who is funding the research?

This study has received a grant from the National Institute for Heath Research (NIHR), which is funded through the Department of Health in the UK to improve the health and wealth of the nation through research.

Who has reviewed this study?

This study has been reviewed by the NHS Research Ethics Committee London – City & East. The National Research Ethics Service protects the rights, safety, dignity and wellbeing of research participants.

The study drugs have authorisation for use from the Medicines & Healthcare products Regulatory Agency (MHRA). The MHRA regulates medicines and medical devices in the UK.

The study has also been reviewed by the NIHR to meet the necessary scientific standards.

Contact details for further information:

If you have any general questions on taking part in research, please contact the Patient Advice and Liaison Service [insert local details here]. The research team can also be contacted directly [insert local details here].

Site Principal Investigator: [details to be inserted here]

Site lead research nurse: [details to be inserted here]

Thank you for considering taking part in this study.

Appendix 6 Delphi exercise

A web-based survey of pain specialists in the UK utilised the Delphi method to determine the choice of needle, injectate and volume of injection, as well as the choice of steroid, dose and volume and the maximum dose of steroid. Of approximately 250 pain specialists consulted, 42 took part in the survey.

TABLE 21 Results of the Delphi exercise

Question	Response (%)	Response count
1. At what maximum steroid dose, do you think, reviewers and general sceptics could claim that a positive result for a facet-joint injection was due to systematic action, rather than local benefit?		
60 mg of methylprednisolone	25.0	10
80 mg of methylprednisolone	22.5	9
100 mg of methylprednisolone	20.0	8
120 mg of methylprednisolone	32.5	13

	Response (%)	Response count
2. Which volume is closest to your choice in each facet-joint?		
< 1 ml	28.6	12
1 ml	38.1	16
1.5 ml	21.4	9

	Response (%)	Response count
3. Assuming that we keep to a maximum of four joints, what steroid dose should we use in each joint?		
10 mg of methylprednisolone per joint	40.5	17
20 mg of methylprednisolone per joint	57.1	24
30 mg of methylprednisolone per joint	2.4	1

	Most likely, % (*n*)	Likely, % (*n*)	Not likely, % (*n*)	Does not affect the outcome, % (*n*)	Rating average	Response count
4. If we were not to use methylprednisolone, which of these two steroids would you prefer?						
Triamcinolone	85.7 (36)	9.5 (4)	2.4 (1)	2.4 (1)	1.21	42
Dexamethasone	12.5 (4)	34.4 (11)	50.0 (16)	3.1 (1)	2.44	32

	Response (%)	Response count
5. The sham group should have a fluoroscopic guided needle placed		
Next to the periarticular surface with no injection	38.1	16
Next to the periarticular surface with saline injected (same volume as the active group)	28.6	12
Intra-articular placement with only contrast injected	21.4	9
Intra-articular placement with contrast and placebo (saline) injection (same volume as the active group)	11.9	5

Appendix 7 Sample case report form

Patient identification number _____

Patient initials _____

Barts Health NHS
NHS Trust

Barts and The London
School of Medicine and Dentistry

CASE REPORT FORM

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

Representative of the Sponsor:

Dr Sally Burtles

Director of Research Services

JRMO

QM Innovation Building

5 Walden Street

London

E1 2EF

Phone: 020 7882 7265

Email: sponsorsrep@bartshealth.nhs.uk

Chief investigator: Dr Vivek Mehta

Site principal investigator:

Co-investigators:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient eligibility – inclusion criteria

Inclusion criteria		
	Yes	No
1. Patient aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific 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		
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		
6. Patient is suitable for the facet- joint feasibility study		

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient eligibility – exclusion criteria

Exclusion criteria		
	Yes	No
1. Patient refusal to consent		
2. More than four painful lumbar facet-joints		
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		
4. 'Red flag' signs including thoracic pain, fever, unexplained weight loss, bladder or bowel dysfunction, progressive neurological deficit, and saddle anaesthesia		
5. 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		
10. Previous lumbar facet-joint injections, spinal surgery or any major trauma or infection to lumbar spine.		
11. Patient 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. Patient unable to commit to the six-month study duration		
14. Patient involved in legal actions or employment or benefit tribunals related to their low back pain		
15. Patient with a history of substance abuse		

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Consent

Date of patient consent _____

Version of consent form used _____

Baseline pain score (NRS) up 7 days preceding recruitment ☐ date taken:

I confirm that this patient is eligible to enter the study _____

(signature of medical doctor on delegation log)

Patient visit schedule

		Date of visit(s)
Visit 1	Screening and informed consent Outcome questionnaires at baseline	
Visit 2	Diagnostic test (medial branch nerve blocks)	
Visit 3	Study procedure (facet-joint injections or sham procedure)	
	Combined physical and psychological programme	Date of first session: Date of last session: Number of sessions attended:
Visit 4	Outcome questionnaires at 6 weeks	
Visit 5	Outcome questionnaires at 3 months	
Visit 6	Outcome questionnaires at 6 months	

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

General health

How long has the patient been aware of his/her non-specific low back pain? _____ Years _____ Months

In general, would the patient describe his/her health as: (tick box)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

Occupation information

What is the patient's current work status? (tick box)

- Full time ☐
- Part time ☐
- Volunteer ☐
- Modified duties ☐
- Disabled ☐
- Not working ☐
- Homemaker ☐
- Retired ☐
- Not applicable ☐

Type of work or occupation: _____

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

Did the patient's illness cause him/her to stop working?

- Yes ☐
- No ☐
- Not applicable ☐

Other (give reason):

_____

If the patient continued working, how many work days in the past 3 months, prior to the procedure, did he/she miss due to pain?

_____ days

What was the patient's level of activity prior to the procedure?

- Hard manual work ☐
- Lifting ☐
- Walking ☐
- Sedentary ☐

Social history

Smoking

- Current smoker ☐

_____ cigarettes/day

- Ex-smoker ☐

_____ date stopped

- Never smoked ☐

Alcohol

_____ Units consumed per week

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

Exercise per week: (tick box)	>5 days	☐
	3-5 day	☐
	1-2 days	☐
	Less than 1 day	☐

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Visit 1

Baseline

Investigator's initials _____

Date _____

Visit 1- Baseline

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Investigator's initials _____

Date _____

Visit 1- Baseline

Patient identification number _____

Patient initials _____

Patient's expectation of benefit

How much improvement in pain does the patient expect from the procedure? (circle one)

1	2	3	4	5	6

Expect no improvement Expect total improvement

Outcome questionnaires

Has the questionnaire pack (set 1) been completed? Yes ☐

No ☐

Investigator's initials _____

Date _____

Visit 1- Baseline

Patient identification number _____

Patient initials _____

Visit 2

Diagnostic test

Investigator's initials _____

Date _____

Visit 1- Baseline

Patient identification number _____

Patient initials _____

Diagnostic test (medial branch nerve blocks)

To be completed by PI

Study centre _____

Date of procedure _____

Time of procedure _____

Operator _____

Procedure details Number of injections _____

IMP injected 1% lidocaine 0.5% per site

Levels injected

Post injection evaluation 1 (20 to 40 minutes after injection)

To be completed by PI

Time of evaluation _____

Minutes after injection _____

Please rate the patient's current level of pain on a numerical rating scale (NRS) of 0-10. (0 is no pain and 10 is worst pain):

Patient's current pain score = ☐

Investigator's initials _____

Date _____

Visit 1- Baseline

Patient identification number _____

Patient initials _____

Post injection evaluation 2 (180 to 240 minutes after injection)

To be completed by PI

Time of evaluation _____

Minutes after injection _____

Please rate the patient's current level of pain on a numerical rating scale (NRS) of 0-10. (0 is no pain and 10 is worst pain):

Patient's current pain score = ☐

Investigator decision: **positive test is a 50% or greater pain relief lasting more than 30 minutes** (circle one)

☐ Positive (for randomisation) **Date of randomisation** _____

☐ Negative (end of study)

Visit 3- Study procedures form the 'blinded CRF'

This section is to be completed by the PI and kept separately in a locked filing cabinet until unblinding

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Blinded CRF

Barts Health NHS
NHS Trust

Barts and The London
School of Medicine and Dentistry

CASE REPORT FORM

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

Representative of the Sponsor:

Dr Sally Burtles

Director of Research Services

JRMO

QM Innovation Building

5 Walden Street

London

E1 2EF

Phone: 020 7882 7265

Email: sponsorsrep@bartshealth.nhs.uk

Chief investigator: **Dr Vivek Mehta**

Site principal investigator:

This section is the 'blinded CRF' to be completed by the PI and kept separately in a locked filing cabinet until unblinding

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Blinded CRF

Visit 3

Study procedure

Study procedure (facet-joint injections or sham procedure)

To be completed by PI

Study centre _____

Date of procedure _____

Time of procedure _____

Operator _____

Procedure details

Number of injections _____

Levels injected

Investigator's initials _____

Date _____

CPP

Patient identification number _____

Patient initials _____

Combined physical and psychological programme

Investigator's initials _____

Date _____

Facet-joint study case report form version 3. 12 Apr 2016

CPP

Patient identification number _____

Patient initials _____

Combined physical and psychological programme

Study centre _____

	Date attended	Outcomes delivered Y/N
Session 1	_____	Y/N
Session 2	_____	Y/N
Session 3	_____	Y/N
Session 4	_____	Y/N
Session 5	_____	Y/N
Session 6	_____	

If all outcomes not delivered please provide further details:

Investigator's initials _____

Date _____

Visit 4 – Outcome measures at 6 weeks

Patient identification number _____

Patient initials _____

Outcomes

6 Weeks Post Intervention

Investigator's initials _____

Date _____

Visit 4 – Outcome measures at 6 weeks

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 4 – Outcome measures at 6 weeks

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 2) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the intervention? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the intervention? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Facet-joint study case report form version 3. 12 Apr 2016

Visit 5 – Outcome measures at 3 months

Patient identification number _____

Patient initials _____

Outcomes

3 Months Post Intervention

Investigator's initials _____

Date _____

Visit 5 – Outcome measures at 3 months

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 5 – Outcome measures at 3 months

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 3) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the last visit? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the last visit? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Visit 6 – Outcome measures after 6 months

Patient identification number _____

Patient initials _____

Outcomes

6 Months Post Intervention

Investigator's initials _____

Date _____

Visit 6 – Outcome measures after 6 months

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 6 – Outcome measures after 6 months

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 4) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the last visit? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the last visit? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Facet-joint study case report form version 3. 12 Apr 2016

End of study

Patient identification number _____

Patient initials _____

End of study

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

End of study

To be completed by research assistant

Date of final study contact with patient _____

Reason (circle one)

- ☐ Completed study
- ☐ Withdrawn from study
- ☐ Other

Reason for withdrawal from study (circle one)

- ☐ Drop out
- ☐ Protocol non-compliance
- ☐ Adverse event (please complete AE form at the end of the CRF)
- ☐ Other

If other, provide further details:

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Adverse events

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Adverse events 1

Date adverse event occurred _____

Date investigator become aware of the event _____

Location of adverse event

_____

Event details:

Is the adverse event related to the procedure? (circle one only)

- ☐ Unrelated
- ☐ Unlikely
- ☐ Possible
- ☐ Probably
- ☐ Related

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Was the adverse event a serious adverse event (SAE)?

- ☐ Yes
- ☐ No (move on to action plan)

Serious criteria (circle all that apply)

- ☐ The AE led or could have led to a congenital anomaly/birth defect
- ☐ The AE led or could have led to death
- ☐ Resulted in medical or surgical intervention to prevent permanent impairment to a body structure
- ☐ Life-threatening illness or injury
- ☐ Resulted in permanent impairment of a body structure or body function
- ☐ Required inpatient hospitalisation
- ☐ Other

Action plan

- ☐ No action required
- ☐ Amend consent form
- ☐ Amend protocol
- ☐ Inform current subjects
- ☐ Terminate or suspend protocol
- ☐ Other

Has the Sponsor been informed?

- ☐ Yes
- ☐ No

If other, provide further details:

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Adverse events 2

Date adverse event occurred _____

Date investigator become aware of the event _____

Location of adverse event

_____

Event details:

Is the adverse event related to the procedure? (circle one only)

- ☐ Unrelated
- ☐ Unlikely
- ☐ Possible
- ☐ Probably
- ☐ Related

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Was the adverse event a serious adverse event (SAE)?

- ☐ Yes
- ☐ No (move on to action plan)

Serious criteria (circle all that apply)

- ☐ The AE led or could have led to a congenital anomaly/birth defect
- ☐ The AE led or could have led to death
- ☐ Resulted in medical or surgical intervention to prevent permanent impairment to a body structure
- ☐ Life-threatening illness or injury
- ☐ Resulted in permanent impairment of a body structure or body function
- ☐ Required inpatient hospitalisation
- ☐ Other

Action plan

- ☐ No action required
- ☐ Amend consent form
- ☐ Amend protocol
- ☐ Inform current subjects
- ☐ Terminate or suspend protocol
- ☐ Other

Has the Sponsor been informed?

- ☐ Yes
- ☐ No

If other, provide further details:

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Investigator's initials _____

Date _____

Appendix 8 Sample adverse event log

ReDA number 008021 BLT
REC number 15/LO/0500
EudraCT number 2014-003187-20

CI: Vivek Mehta
Study name: Facet- Joint Study
IMP used in trial: Depo-Medrone, Bupivicaine

Adverse Event and Serious Adverse Event log

Event no.	Site	Subject no.	Event type (please see final page for definitions)	Related to IMP? (Y/N)	Expected reaction to IMP? (Y/N)	AE/SAE/ SUSAR?	Date of onset	Body system	Event description	Outcome (please see final page for outcome options)	Resolved? (Y/N)
1											
2											
3											
4											
5											
6											
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AE & SAE log v1, 5th Dec 2014

Event types

An Adverse Event (AE) is defined (according to CPMP/ICH/377/95) as "*Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*". Any adverse event which affects a participant from the time they give informed consent to 30 days after the last study related contact (as defined in the protocol) should be recorded.

An adverse event is defined as serious if it:

1) Results in death
2) Is life threatening
3) Requires inpatient hospitalisation or prolongation of existing hospitalisation
4) Results in persistent or significant disability/incapacity, or
5) Is a congenital anomaly/birth defect

Please indicate one of these 5 types in the "Event type" column for all SAEs and SUSARs.

An SAE is defined as a SUSAR if it may be related to, and is an unexpected reaction to, the study intervention.

Outcomes

For the "Outcome" column, please indicate one of the following outcomes of the event:

1) Resolved
2) Resolved with sequelae
3) Improved
4) Persisting
5) Worsened
6) Fatal
7) Unknown

Appendix 9 Literature review to inform the health economics component and costing methodology

Literature review

Objectives

A rapid, systematically based review of the health economics literature was conducted to inform the development of the framework for an economic model to assess the longer-term cost-effectiveness of FJIs for persistent non-specific LBP. The review identified, and assessed the scope and quality of, the current evidence in relation to:

1. the cost-effectiveness of FJIs for persistent non-specific LBP
2. specific resources and associated costs associated with FJIs
3. relevant outcomes to inform a health economic analysis, for example health-related quality of life/utilities – this considered possible candidate measures used elsewhere, for example the EQ-5D or SF-6D
4. possible frameworks, for example economic models, that have been reported in the literature.

Methods

A PICO (problem/population, intervention, control, outcomes) approach was used to generate appropriate search terms (*Table 22*). PubMed and the NHS Economic Evaluation Database (NHS EED) were systematically searched to identify relevant studies (systematic reviews, randomised controlled trials and, when necessary, observational studies), following key PRISMA principles.[13]

Cost of illness studies, costing studies or other partial economic evaluations were identified but not formally reviewed. In addition, searches to identify literature to inform health-related quality of life/utility estimates were undertaken.

Results

The search strategy identified only two studies[65,66] evaluating the cost of FJIs, although these were partial economic evaluations rather than formal cost-effectiveness studies, and one study[37] evaluating health-related quality of life.

Cohen *et al.*[65] evaluated lumbar z-joint denervation costs and outcomes using three paradigms: (1) radiofrequency denervation without the use of a screening block; (2) radiofrequency denervation if the patient obtained significant relief after a single diagnostic block; and (3) radiofrequency denervation only if an appropriate patient had a positive response to two confirmatory medial branch (facet-joint nerve) blocks to determine which treatment paradigm was associated with the highest overall and radiofrequency

TABLE 22 The PICO framework for the health economics literature review

Number	Problem/population	Intervention	Control	Outcomes
1.	facet-joint	injection	sham	cost
2.	cervical	analgesia	placebo	effectiveness
3.	thoracic	denervation	standard of care	economic
4.	lumbar			quality of life
5.				utilities

denervation success rates, and to evaluate the relative costs per successful treatment for each of the three groups. The primary end point as a measure of 'clinical success' was 3 months of significant pain relief. The cost of a diagnostic facet-joint block averaged US$350 for the first level and US$170 for each subsequent level; the cost of radiofrequency denervation averaged US$650 for the first joint and US$325 for each additional joint; the overall group success rate ranged between 17% and 32%; and the mean cost of successful treatment in the single-block group was US$5172 (SD US$860). The study found that proceeding straight to radiofrequency denervation without any diagnostic blocks was associated with both the lowest cost per successful procedure and the highest number of total successful procedures.

Burnham *et al.*[66] conducted an evaluation of the effectiveness of radiofrequency denervation of the lumbar facet-joints for pain, analgesic intake, disability, patient satisfaction, back pain-related costs and employment status in patients with chronic LBP of facet-joint origin in the context of a clinical audit of a new radiofrequency denervation programme. Both direct and indirect costs relating to LBP care that were or could potentially be borne directly by the subject were estimated. Direct costs were calculated by asking the subject to describe the type and number of any of the following treatments/services received for his or her LBP in the previous month: physician office visits, chiropractic treatments, physiotherapy treatments and treatments from other allied health practitioners (massage, acupuncture, psychology and so forth).

Post radiofrequency denervation, significant improvements were observed in pain, analgesic requirements, satisfaction, disability and direct costs occurred. These outcomes peaked at 3–6 months and gradually diminished thereafter. Satisfaction with medical care and living with current symptoms improved similarly. Overall, satisfaction with the radiofrequency denervation procedure was high and no complications were reported.

Based on these outcomes, it was deemed that radiofrequency denervation provides safe and significant short-term improvements in pain, analgesic requirements, function, satisfaction and direct costs in patients with chronic LBP of facet origin.

Ribeiro *et al.*[37] studied 60 subjects with a diagnosis of facet-joint syndrome who were randomised into an experimental group (intra-articular injection of six lumbar facet-joints with triamcinolone hexacetonide) or a control group (intramuscular injection of six lumbar paravertebral points with triamcinolone acetonide). No details were provided by the authors on trade names or manufacturer details for the drugs used. Outcome measures including a pain VAS, a pain VAS during extension of the spine, a Likert scale, an improvement percentage scale, the Roland Morris Disability Questionnaire and the SF-36 were administered at baseline and at 1, 4, 12 and 24 weeks after the interventions. The data revealed an improvement in the experimental group in terms of health-related quality of life, in the 'role physical' profile, assessed by the SF-36.

Conclusions

The literature search identified a very limited set of evidence on the cost-effectiveness of diagnostic or therapeutic FJIs and the studies identified were simple costing studies. As such, a knowledge gap remains for the simulation of longer-term outcomes to inform cost-effectiveness models with long-term horizons.

Resource use associated with facet-joint injections

Resource use: methodology

The patient questionnaire was completed by a research assistant during visits to a nurse-led outpatient pain management clinic and took approximately 1 hour to complete. The visits took place at 6 weeks (visit 4, research study-specific visit), 3 months (visit 5, research study-specific visit) and 6 months (visit 6, standard routine consultant-led outpatient check-up).

The questions regarding NHS resource use specifically asked about the most likely health-care professionals who would be engaged with during treatment for LBP; the results are detailed in *Table 23*.

TABLE 23 NHS resource use reported via the case report form patient questionnaire

Coded variable	Variable type	Description of resource use and basis for the unit cost	Unit cost	Unit cost source
V01 _ Emergency DepartmentVisits	Number, long integer	Emergency department visit (standard A&E attendance)	£137.74	Department of Health[68]
V01 _ LengthOfStay	Number, long integer	Length of stay in hospital (emergency admission as a result of serious adverse event)	Unit cost method to be decided – see data. National average unit cost: Non-Elective Inpatients – Long Stay £3058.14, Non-Elective – Short Stay £615.83	Department of Health[68]
V01 _ GPAppointments	Number, long integer	GP appointment (assumed to be a standard GP consultation with an average contact of 9.22 minutes) at a GP surgery	£36	Curtis and Burns[67]
V01 _ PainClinic	Number, long integer	Pain clinic (standard routine outpatient appointment at a pain management clinic)	Assumed to be consultant led unit cost – £148.03 (non-consultant-led unit cost £111.15)	Department of Health[68]

A&E, accident and emergency.

Medication

The patient questionnaire contained within the case report form collected information on current prescribed analgesics and any other medications at baseline. At the three follow-up time points information on current analgesics and other medications was also collected along with any changes in medication during the follow-up period. Information on medication use is reported in *Table 24*.

The specific dates that prescriptions were issued, including the dates that any changes in medication occurred, are unknown as medications were prescribed by the patients' GPs rather than by the trial team. Medication reported in the 'other' medication category that was not related to the treatment of LBP was excluded.

Medication costs were calculated at baseline (visit 1) to evaluate the pain medication being taken before the intervention commenced. Costs were then calculated between baseline and the 6-week follow-up (visit 4), between visit 4 and the 3-month follow-up (visit 5) and between visit 5 and the 6-month follow-up (visit 6). As some patients had their pain medication prescriptions changed in the community by their GP between follow-up visits to the hospital, any change in prescription was assumed to be at the mid-point between follow-up visits for costing purposes. *Table 25* shows how the time periods were classified in days to calculate the duration of prescribed medication.

The cost of medication per day was calculated and this was then multiplied by the number of days the medication was prescribed.

TABLE 24 Medication use reported via the case report form patient questionnaire

Coded variable	Variable type	Description of resource use and basis for the unit cost	Unit cost source
V01 _ CurrentAnalgesics	Text	Current analgesics (name of medication, dosage and frequency)	BNF[69]
V01 _ OtherMedications	Text	Other medications (name of medication, dosage and frequency)	BNF[69]

BNF, *British National Formulary*.

TABLE 25 Calculating the length of a prescription for analgesic medication

Time period[a]	Duration in days
Duration of baseline prescribed medication	A period of 21 days before the baseline assessment (assumption as pretrial duration of prescribed medication is unknown)
When the same medication was reported at successive follow-up points the whole period between time points was considered as a continuous prescription	Baseline (visit 1) to 6-week follow-up (visit 4) = 42 days; 6-week follow-up (visit 4) to 3-month follow-up (visit 5) = 51 days; 3-month follow-up (visit 5) to 6-month follow-up (visit 6) = 93 days
When a change in prescribed medication was reported an approximate mid-point between follow-up visits was used to estimate prescription duration – the previous medication was allocated the first half of the number of days in that period and the new medication was allocated the second half of the number of days during that time period	At visit 4: old medication = first 21 days after baseline assessment, new medication = the 21 days before visit 4; at visit 5: old medication = first 25.5 days after visit 4, new medication = the 25.5 days before visit 5; at visit 6: old medication = first 46.5 days after visit 5, new medication = 46.5 days before visit 6

a Total of 180 days or 6-month duration of the trial (assumed 30-day months).

Dealing with missing medication data

Table 26 contains the substitute costing rules applied when reported medication prescriptions were vague or information was missing. *Table 27* lists the analgesic medication reported by trial participants and the accompanying unit costs.

Calculating quality-adjusted life-years

For both groups in the study the number of QALYs gained was calculated for the complete cases for the 6 months between baseline (before treatment) and the final 6-month follow-up visit, as shown in *Table 28*.

Existing measures used to collect resource use data in lower back pain studies

A search of the DIRUM[82] to compare existing resource use measures specifically related to LBP was conducted. The results of this search are shown in *Table 29*.

TABLE 26 Substitute costing rules for vague or missing information on medication dose and frequency

Medication dose and frequency of dose is reported within a possible range depending on need	The lower dose and frequency is used as a conservative estimate or a maintenance dose is used
Ibuprofen (200 mg)	The daily standard maintenance dose is used = two tablets, three times per day = six tablets = 1.2 g per day
Paracetamol (500 mg)	The daily standard dose of 500 mg every 4 hours = six tablets per day = 3 g per day
Co-codamol (30/500 mg)	A standard dose of two tablets four times a day = eight tablets per day
Naproxen (250 mg)	A standard maintenance dose of one tablet every 6 hours = four tablets per day = 1 g per day

TABLE 27 Medications reported and accompanying unit costs[a]

Name of medication	Dose	Frequency of dose	Unit cost per pack (£)	Number of tablets per pack	Cost per tablet (£)
Amitriptyline	10 mg	3 × (at night)	0.96	28	0.034286
Amitriptyline	25 mg	1 × daily	0.99	28	0.035357
Amlodipine	5 mg	1 × daily	0.91	28	0.0325
Co-codamol	30 mg	Two tablets each 4 × daily	6.73	100	0.0673
Co-codamol	8/500 mg	4 × daily	1.16	30	0.038667
Co-codamol	30/500 mg	Daily as required	6.73	100	0.0673
Codeine	30–60 mg	BD (2*)/TDS (3*), depending on severity	1.44	28	0.051429
Codeine phosphate	30/500 mg	6 × daily	6.73	100	0.0673
Diazepam	5 mg	1 × nightly	1.06	28	0.037857
Duloxetine	60 mg	1 × nightly	27.72	28	0.99
Duloxetine	60 mg	1 × daily	27.72	28	0.99
Gabapentin	200 mg	2 × daily	3.17	100	0.0317
Ibuprofen	5% gel	3 × daily	1.28	1	1.28
Ibuprofen	400 mg	3–4 × daily	3.50	84	0.041667
Lyrica	300 mg	Max. 300 mg per day for neuropathic pain	64.40	56	1.15
Naproxen	As needed	Assumed standard dose	1.12	28	0.04
Nortriptyline	10 mg	1 × daily	12.06	100	0.1206
Palexia	(50 mg)	2 × daily	12.46	28	0.445
Paracetamol	500 mg as required	Assumed standard dose	0.92	32	0.02875
Pregabalin	75 mg standard	3 × daily, standard dose 75 mg twice daily	64.40	56	1.15
Solpadol	Assumed standard dose	Assumed standard dose	6.74	100	0.0674
Tremadol (assumed tramadol)	50 mg	2 × every 4–6 hours	1.20	30	0.04

BD (2*), two times per day; max., maximum; TDS (3*), three times per day.
a Costed according to the *British National Formulary*.[69]

TABLE 28 Calculation of QALYs

Time period	Calculation method
6 weeks between baseline (visit 1) and 6-week follow-up (visit 4)	[(EQ-5D mean utility at visit 1 + EQ-5D mean utility at visit 4)/2] × (6 weeks) = QALYs gained at visit 4
6 weeks between 6-week follow-up (visit 4) and 3-month follow-up (visit 5)	[(EQ-5D mean utility at visit 4 + EQ-5D mean utility at visit 5)/2] × (6 weeks) = QALYs gained at visit 5
12 weeks between 3-month follow-up (visit 5) and 6-month follow-up (visit 6)	[(EQ-5D mean utility at visit 5 + EQ-5D mean utility at visit 6)/2] × (12 weeks) = QALYs gained at visit 6
Total QALYs gained at the end of treatment	QALYs gained at visit 4 +QALYs gained at visit 5 +QALYs gained at visit 6

TABLE 29 Existing resource use measures for lower back pain

Disease category	Reference	Items of resource use being measured
Anaesthesia and pain control	Back Pain Questionnaire[91]	GP visits, physiotherapy visits, other NHS (osteopath and chiropractor visits)
Anaesthesia and pain control	BeST trial follow-up questionnaire[44]	GP visits, inpatient admissions, practice nurse visits, outpatient attendance, medication, A&E attendance, physiotherapy visits, psychologist visits, other NHS (scans, radiography, blood tests), other non-NHS (private visits: chiropractor, osteopath, physiotherapist, alternative therapy, etc.)
Anaesthesia and pain control	Lower Back Pain Resource Use Questionnaire[92]	Inpatient admissions, outpatient attendance, A&E attendance, employer,[a] physiotherapy visits, health-care aids, other non-NHS (chiropractor, acupuncturist and osteopath visits)
Anaesthesia and pain control, orthopaedics and trauma	Scottish Back Trial Questionnaire[93]	GP visits, inpatient admissions, outpatient attendance, medication, physiotherapy visits

A&E, accident and emergency.
a This refers to the effect that lower back pain has on employment/current job role.

Appendix 10 Summary of changes to the protocol

Amendment	Protocol version, date	Summary of changes
Minor amendment	4, 4 February 2015	Update to schedule of assessment table
Substantial amendment 1	5, 2 September 2015	Update to patient safety information
		Revised details for the TSC and DMC
Substantial amendment 2	6, 7 May 2016	Change of Chief Investigator and Principal Investigator at Barts Health NHS Trust
		Lidocaine renamed as a non-IMP
		Additional recruitment from spinal orthopaedic and musculoskeletal clinics

Appendix 11 Missing or incomplete questionnaire data

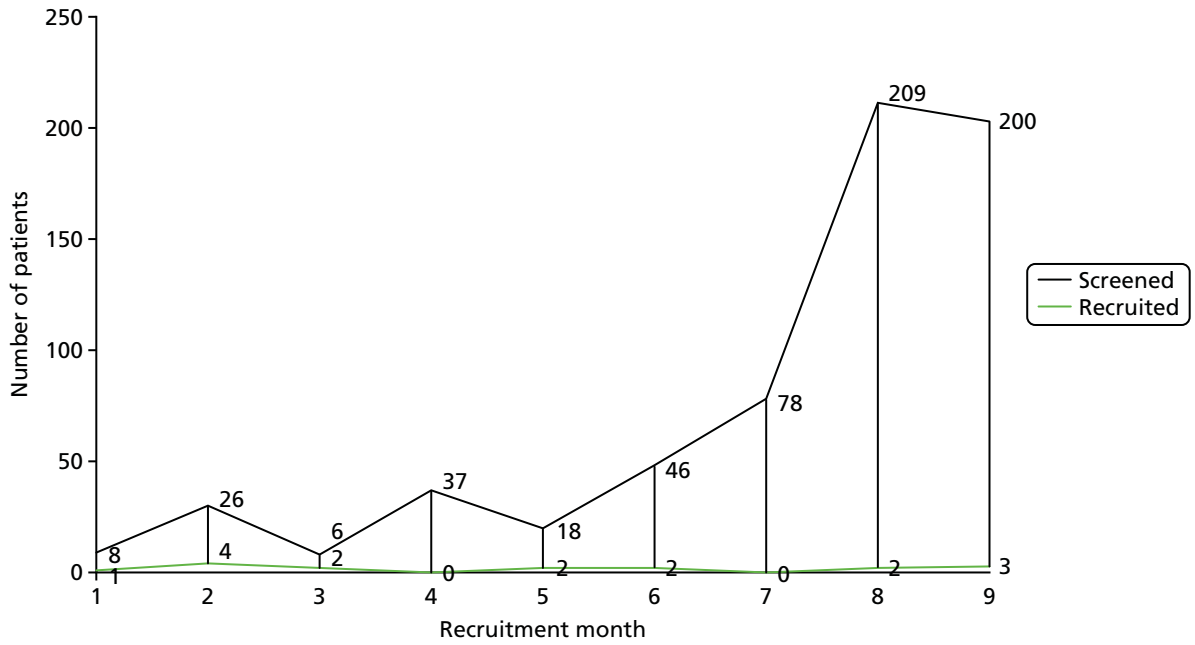
Eleven participants did not complete, or completed incorrectly, the different components of each questionnaire; this is detailed in *Table 30*.

TABLE 30 Missing or incomplete questionnaire data

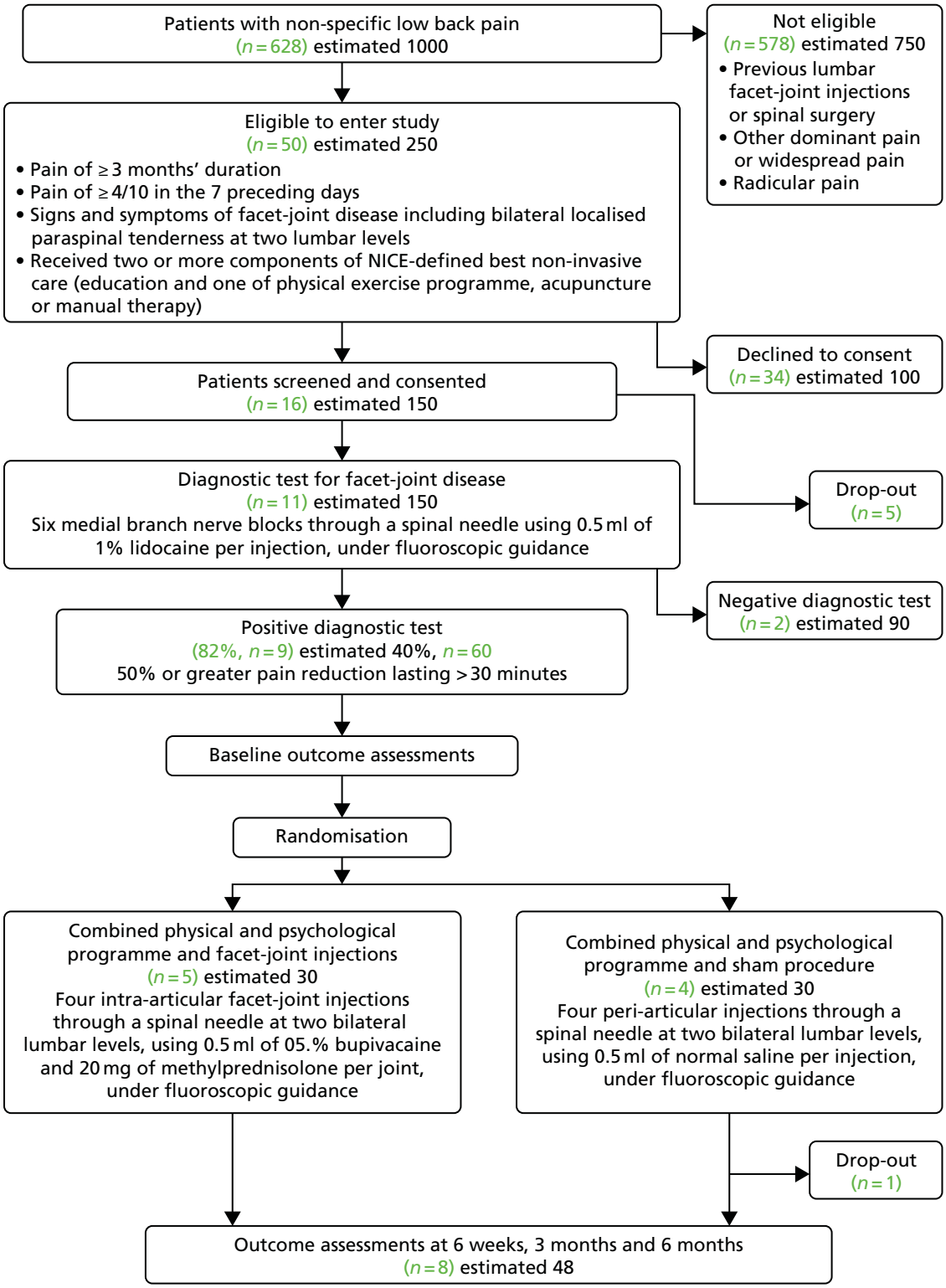
Participant number	Missing data				Details
	Baseline	6 weeks	3 months	6 months	
1002		All	All		
1003		BPI			'What treatments or medications are you receiving for your pain?' – missing
1004				BPI	'Please mark on the diagram the area of your pain' – spoiled
1005	SF-12				'Climbing several flights of stairs' – missing
1006			All		
1007	Oswestry				'Social life' – spoiled
1009		All			
1009	SF-12				'Physical health, limited to work, emotional problems, did work less carefully' – missing
1010	SF-MPQ-2				'Hot burning pain, splitting pain' – missing
	SF-12				'Did work less carefully' – missing
	Oswestry				'Personal care, sleeping' – spoiled; 'sex life' – missing
1011	SPS 6				'I felt hopeless about finishing certain work tasks, due to my health problems', 'At work, I was able to focus on achieving my goals despite my health problem' and 'Despite having my health problem, I felt energetic enough to complete all my work' – missing
1014	EQ-5D-5L				'Pain/discomfort' – missing
	Oswestry				'Sex life' – missing

Oswestry, Oswestry Low Back Pain Disability Questionnaire.

Appendix 12 Graph showing the number of patients screened compared with the recruitment rate by recruitment month



Appendix 13 Flow diagram showing the actual compared with the estimated flow of participants through the study



Appendix 14 Limitations of current resource use measures and recommendations for improving the accuracy of capturing future NHS service provision

Resource use	Limitations and recommendations
Medication	Limitations: • No data were collected on the duration of time that medication was prescribed for – specifically, there was no accurate information on the date that medication was prescribed or the length of time that each prescription was intended for. As pain medication can be taken for a prolonged length of time, each repeat prescription should also be noted for accurate costing • Information on the dose and the number of times per day that the dose is to be taken was sometimes vague or missing Recommendations: • The prescribed dose, the prescribed number of times per day that the dose is to be taken and the number of days per prescription should be documented • Ensure that the names of medications are accurate
Visits to health-care professionals	
Time scale of data capture at follow-up	Limitation: • The follow-up periods were 6 weeks, 3 months and 6 months post intervention. However, the question on the case report form asked patients to report visits to health-care professionals within the last 4 weeks prior to the follow-up data collection session. This would not capture visits prior to that 4-week window Recommendation: • Amend the question regarding duration to include the whole period before the follow-up data collection session to capture all resource use information

Hospital inpatient stay	Limitation: no information on mode of admission or reason for admission
	Recommendation:
	• To facilitate the costing of secondary care resource use, sufficient clinical information should be collected so that the correct Healthcare Resource Group (HRG) codes from NHS reference costs can be used for accurate costing. Such information includes the following:
	  ○ Mode of admission:
	  – elective inpatient admission mean cost, £3749.81
	  – non-elective inpatient admission short stay (< 24 hours in hospital) mean cost, £615.83
	  – non-elective inpatient admission long stay (≥ 1 day/night in hospital) mean cost, £3058.14
	  – day case/surgery mean cost, £733.31
	  ○ Clinical reason for admission:
	  – review HRG codes in advance to select the most pertinent to the trial procedure/population

Resource use	Limitations and recommendations
Emergency/A&E attendances	Consider the type of service that trial participants are likely to require. Would they be admitted or treated and discharged? What is the level of investigation and treatment? Treatment and discharge is less costly than treatment and admittance. The construction of appropriate questions to capture information on attendance should be considered if this area of health-care resource use is an important driver of costs for the trial population. If not considered an important cost driver an average cost of £137.74 per attendance can be applied for simplicity
Ambulance service	Consider if trial participants would be potential users of the ambulance service and the implications of service type and associated costs: • Calls, £7 • Hear and treat or refer, £34 • See and treat or refer, £181 • See and treat and convey, £236
Outpatient clinics	Note in advance the type of service-led clinic if relevant. For example, a consultant-led outpatient clinic is more expensive than a non-consultant-led clinic
GP consultations	Limitation: • No information on mode of consultation Recommendation: • GPs consult with patients in various ways, which is particularly important for patients with long-term chronic conditions • Patient attends GP practice appointment, £36 • GP telephone call to patient, £14.60 • GP visits patient at home, £45 (2015 unit price)

A&E, accident and emergency.
Secondary care, hospital-based costs were derived from *NHS Reference Costs 2015 to 2016*.[68] Contains public sector information licensed under the Open Government Licence v3.0.
Primary care GP costs were derived from Curtis and Burns.[67]

EME
HS&DR
HTA
PGfAR
PHR

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