

CLINICAL TRIAL PROTOCOL

Supraneural versus Infraneural Approach to transforaminal Epidural Steroid injection for unilateral lumbosacral radicular pain (SIAMESE): a study protocol for a randomised non-inferiority trial

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Abstract

Background: Lumbosacral radicular pain is commonly treated by transforaminal steroid epidural injection. There are two methods: the supraneural and the infraneural approaches. The supraneural approach can result in rare but catastrophic consequences from injury to the radiculomedullary artery. The infraneural technique avoids the artery; both approaches show efficacy and are used locally.

Methods: This is a protocol for a randomised, single-blinded, non-inferiority trial of infraneural vs supraneural transforaminal epidural injection for lumbosacral radicular pain at a tertiary referral pain management clinic. Adult patients ($n=92$) with moderate-to-severe lumbosacral radicular pain of >3 months duration, scheduled for transforaminal epidural steroid injection, will be randomised to epidural by either the infraneural or supraneural approach. Only the treating physicians will know which route is used. The primary outcome measure is the differential impact on pain intensity score at 3 months. Secondary outcome measures will include disability and function scores, sleep and activity measures, and adverse events. Participants will be followed up for 12 months.

Conclusions: This study will determine whether the techniques are comparable and, if so, will enable recommendations for the use of an approach without risk of artery damage and catastrophic injury.

Clinical trial registration: ISRCTN 36195887.

Keywords: epidural; lumbosacral radicular pain; non-inferiority; randomised controlled trial; steroid

Lumbosacral radicular pain affects both men and women and is estimated to have a prevalence of about 3–5% of the population, most commonly in middle-aged individuals. The most common cause is nerve irritation secondary to a prolapsed intervertebral disc. It can be associated with facet or ligamentous hypertrophy, spondylolisthesis, or even neoplastic and infectious processes.¹

The standard interventional treatment for lumbosacral radicular pain secondary to prolapsed disc is either a transforaminal epidural steroid injection or microdiscectomy; a recent trial recommended epidural steroid as the first invasive treatment option.² The therapeutic benefits of steroids are thought to arise from their anti-inflammatory properties. In

addition, steroids may provide a stabilising effect on the nociceptive signalling in C-fibres and suppression of ectopic neural discharge.^{3,4} Injections into the epidural space can be achieved using one of three routes: caudal, interlaminar, or transforaminal. The transforaminal route is best suited for targeted delivery of the steroid closer to the site of inflammation at the nerve–disc interface. Several systematic reviews and meta-analyses^{5–7} report good efficacy of the transforaminal approach for delivery of steroid medications to the anterior epidural space via the neural foramen.

Currently, the supraneural transforaminal approach is considered the standard technique. In this approach, the

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needle is directed through the 'safe triangle' under the inferior surface of the pedicle and superolateral to the spinal nerve to reach the anterior epidural space. It is deemed the safe triangle as there is a low risk of damaging the nerve, dorsal root ganglion, or dura mater. The needle trajectory is through the upper third of the intervertebral foramen.⁸ Another approach is the infraneural method, which targets the inferior one-third of the foramen, at the level of the intervertebral disc–nerve interface (Fig 1). A retrospective case review concluded that the infraneural approach appeared to be superior to the supraneural route for unilateral lumbosacral radicular pain caused by a herniated disc, with a minor benefit in terms of disability score.⁹ In addition, the infraneural approach has been found to be not inferior to the supraneural approach for short-term effects in patients with spinal stenosis.¹⁰

There have been several reports of paralysis after supraneural transforaminal epidural steroid injections.^{11,12} Fourteen cases of paraplegia have been reported in the literature, but because there are no accurate records available regarding image-guided lumbar steroid injections, case reports may underestimate the true number of poor outcomes, so the rate of neurological complications is likely to be inaccurate.¹³ The use of the infraneural approach to avoid the radiculomedullary arteries has been recommended.^{8,11,13,14}

Although using the infraneural approach for transforaminal epidural reduces the risk of injury to the radiculomedullary arteries, thereby reducing the risk of potential catastrophic life-changing injury, and in spite of evidence that both supraneural and infraneural are effective, the supraneural approach is regarded as standard and is more widely used.

Our trial is designed to exclude inferiority of the infraneural approach^{15,16} for epidural steroid injection in patients with lumbosacral radicular pain secondary to a prolapsed disc (sciatica). This protocol paper follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.¹⁷

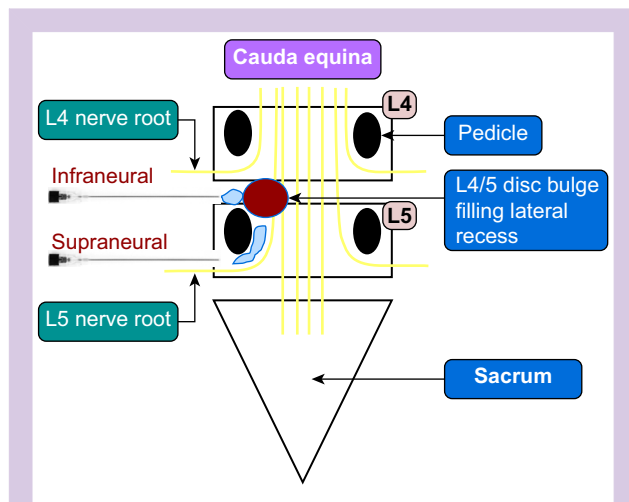


Figure 1. Schematic diagram showing the two epidural approaches to treat the L4/5 prolapsed disc ('disc bulge'). The spread of the steroid is shown in blue.

Methods

Study design

This is a single-centre, single-blind, randomised non-inferiority trial of two approaches for transforaminal epidural steroid injection. The study has been categorised by the Medicines and Healthcare products Regulatory Agency (MHRA) as a Clinical Trial of an Investigational Medicinal Product (CTIMP) because of the 'off licence' epidural injection of steroid, despite this being routinely used in clinical practice.

Inclusion criteria

The following eligibility criteria must be fulfilled for participation in the trial:

- (i) Aged 18 yr or over.
- (ii) Sciatica secondary to prolapsed intervertebral disc with at least 3 months of symptoms and scheduled for epidural steroid injection.
- (iii) Leg pain of 5 or more on a 0–10 numerical rating scale (NRS) for average pain, not responsive to at least one form of conservative treatment.
- (iv) Diagnosis confirmed by MRI showing paracentral disc bulge filling the lateral recess.

Exclusion criteria

- (i) Sciatica attributable to fixed lesions, such as facet or ligamentous hypertrophy, far lateral disc bulge, spinal stenosis, or spondylolisthesis.
- (ii) History of epidural steroid injection in the last 12 months.
- (iii) History of spinal surgery at any lumbar levels.
- (iv) Serious neurological deficit defined as motor impairment of a lower limb, which interferes with activities of daily living.
- (v) Anatomical abnormalities posing technical challenges or contraindication to one of the injection routes and precluding randomisation to epidural approach.
- (vi) Active metastatic disease.
- (vii) Cancer or infection as a cause of back pain.
- (viii) Pregnancy.

Eligibility will be determined at initial screening before consent and randomisation. All randomly allocated participants will be included in the intention-to-treat analysis.

Recruitment and screening

Potentially eligible patients will be identified by a member of the clinical care team and sent an information pack containing a letter of invitation, the participant information sheet, and a reply slip with prepaid envelope to return their contact details to the research team. Written informed consent will be obtained before randomisation. We will keep a screening log of eligible patients.

Informed consent

A delegated, trained member of the research team will obtain written informed consent from participants and provide full details of the trial. It will be made clear that participants will receive their epidural injection regardless of participation, but that neither they nor their doctor will be able to choose the

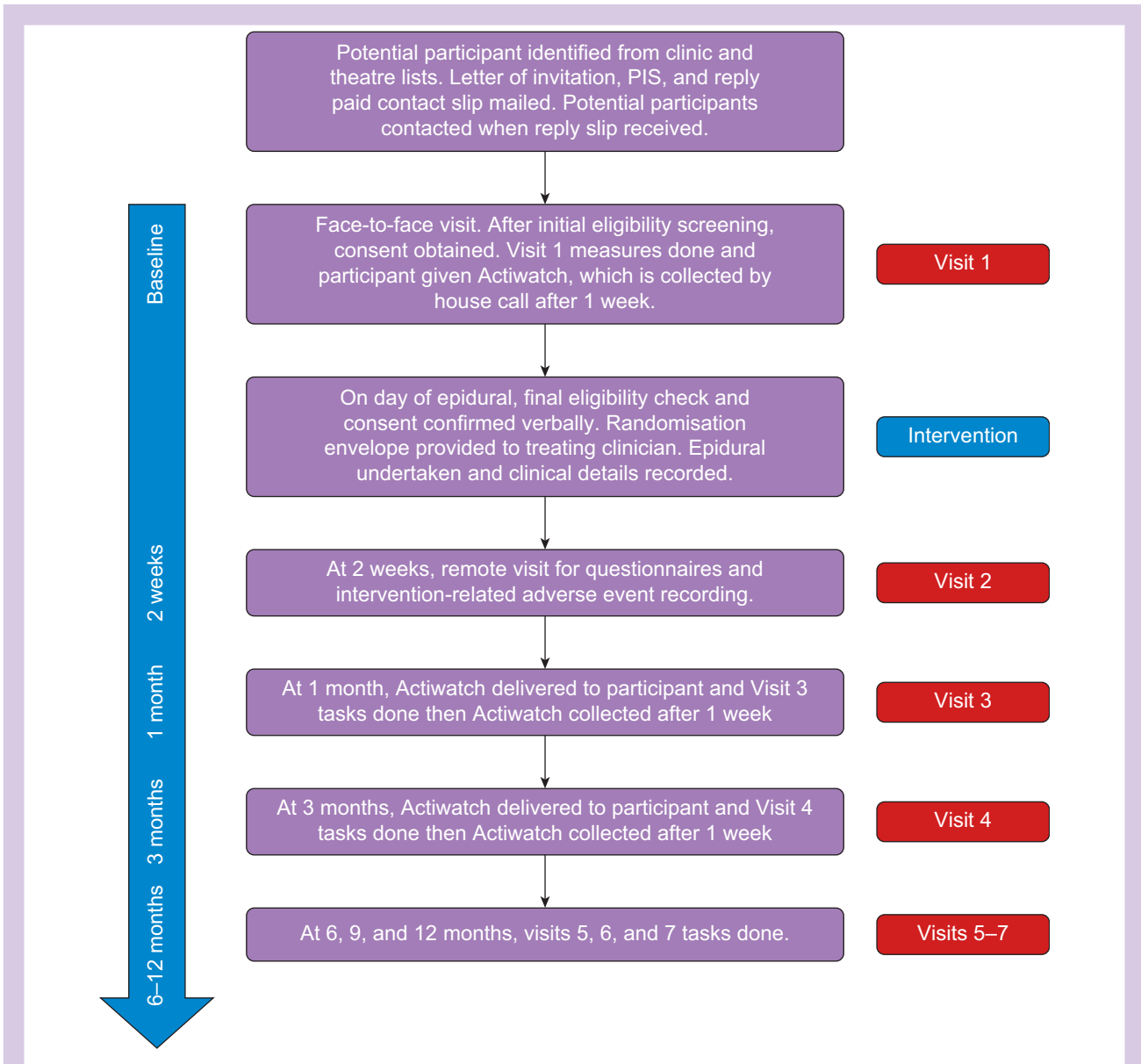


Figure 2. Study flowchart showing recruitment processes and timing.

type of epidural used. All participants can withdraw from the trial at any time, but where possible, consent will be obtained after withdrawal to access medical data for follow-up purposes. The study process flow diagram is presented in Fig 2.

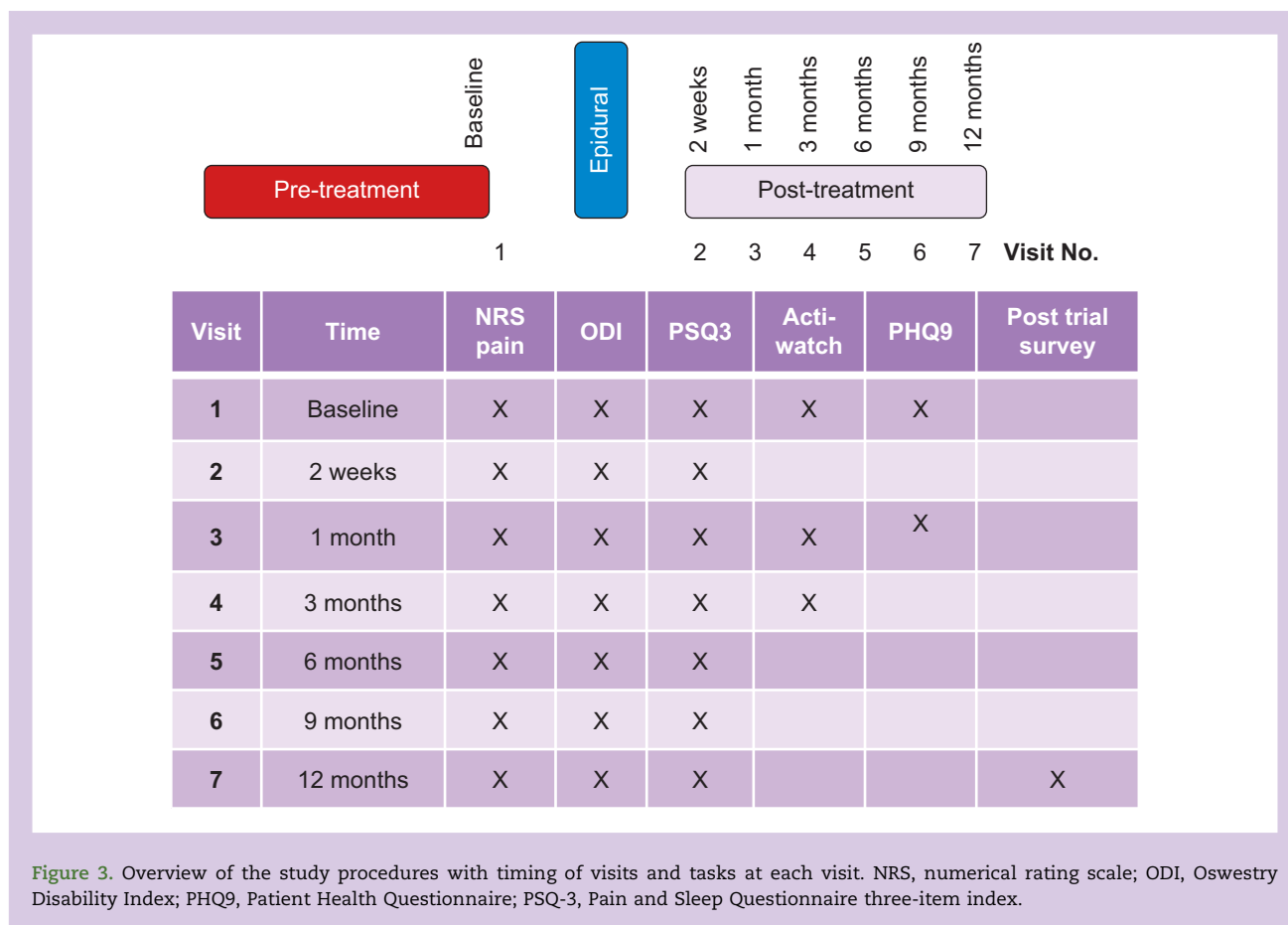
Intervention

Participants will receive transforaminal epidural steroid injection as per routine clinical care. Radiological confirmation of the level of the prolapsed intervertebral disc targeted for treatment will be documented. Epidural injections will be carried out according to a standardised protocol. For supra-neural transforaminal epidural steroid injection, foraminal entry/needle placement will be one level below the radiologically confirmed level. For infraneural transforaminal epidural steroid injection, the foraminal entry/needle placement will be at the same level as the radiologically confirmed level. Digital

subtraction angiography will be used at the discretion of the clinician. Participants will receive contrast (omnipaque), local anaesthetic (levobupivacaine to a maximum of 5 mg), and steroid (dexamethasone solution to a maximum of 10 mg) as per routine clinical care. Epidural dexamethasone is used off-label as a widely accepted practice within the NHS and will be sourced directly from operating theatre stock.

All the clinicians who will be involved in the trial have a minimum of 10 years' experience as chronic pain consultants and will be competent with both approaches. Only clinicians who are competent and willing to adhere to randomisation will be involved. Successful placement of the epidurals will be scored by review of images by three other clinicians.

Before attending for epidural, participants will complete baseline NRS pain scores, a subjective sleep questionnaire (Pain and Sleep Questionnaire three-item index, PSQ-3¹⁸),



physical functioning scores (Oswestry Disability Index, ODI¹⁹), and the Patient Health Questionnaire (PHQ-9²⁰). They will also wear a Philips Actiwatch Spectrum PRO (Linton Instrumentation, Diss, Norfolk, UK), a wrist-worn device providing objective measurements of sleep and activity for 1 week and enabling input of daily pain scores.²¹ These measures will be repeated at various time points (Fig 3) up to 12 months after the epidural injection.

Primary outcome measure

The primary outcome measure is the difference in the average pain intensity NRS scores between the two treatments at 3 months after epidural injection.

The secondary outcome measures include:

- (i) Pain intensity scores at 2 weeks and 1, 3, 6, 9, and 12 months.
- (ii) Objective sleep variables and activity at 1 and 3 months.
- (iii) Subjective sleep variables at 2 weeks and 1, 3, 6, 9, and 12 months.
- (iv) Physical functioning scores at 2 weeks and 1, 3, 6, 9, and 12 months.
- (v) Adverse events.
- (vi) Duration of efficacy and requirement for additional treatments.

Sample size and data analysis

The sample size calculation is based on a minimum clinically relevant difference of 0.5 on the 0–10 NRS average pain score

at 3 months after epidural injection and assumes a maximum standard deviation of 0.7. To achieve power of 80%, allowing for 30% dropout, we will recruit 46 participants per group. The effect of treatment will be analysed on an intention-to-treat basis with treatment-received and per-protocol analyses as required. Between-treatment and within-patient longitudinal data will be analysed using linear mixed effects models, and the influences of confounders, such as age, sex, number, and classes of analgesics used, will be assessed. Data will be analysed using Number Cruncher Statistical Systems (NCSS) version 2020 (NCSS Inc., Kaysville, UT, USA) and Stata 17.0 (StataCorp Inc., College Station, TX, USA). Significance will be defined at one-sided $P < 0.025$ for non-inferiority and $P < 0.05$ (two-sided) otherwise. There will be no interim analysis.

Randomisation

Participants will be randomly assigned (1:1) to one of the two types of epidural injections immediately before the epidural. A schedule will be drawn up by an external statistician, and sealed envelopes will be pre-prepared according to this schedule by a member of staff not involved in the trial. The researcher will select the correct envelope for the participant ID number and personally hand this to the treating clinician immediately before the operating theatre session.

Blinding

The participants and research staff undertaking trial assessments and data analysis will be blinded to allocation. Only the

treating clinician will be aware of which epidural technique is used for an individual participant, and the treating clinicians will not be involved in data analysis. Blinding will be maintained unless it is considered necessary to unblind for safety reasons. The randomisation schedule master file will be held securely by the external statistician, and a sealed hard copy will be stored securely in a locked filing cabinet in a locked office within a restricted-access university building to which designated trial staff only have access if required for unplanned unblinding. The allocation and the actual epidural technique used will also be recorded in patients' clinical notes and can be accessed if necessary.

Trial management and data monitoring

The trial is jointly sponsored by the University of Aberdeen and NHS Grampian. The trial will be managed by the investigators and the research team. Independent trial monitoring and data and safety monitoring committees, comprising external and internal experts, with statistical input and patient representation, have been established. The trial will be monitored by NHS Grampian.

Patient and public involvement

The protocol has been reviewed by members of a local chronic pain support group 'Affa Sair' which is a registered charity with 590 members. The participant-facing information was amended in response to patients' comments. There will also be patient representation on the external monitoring committees, and participants will be asked to complete a questionnaire to tell us their views about taking part in the trial.

Adverse events

Specified expected adverse events at 2 weeks after epidural injection will be recorded plus all other adverse events for 12 months.

Confidentiality

All study staff will comply with the requirements of the UK data protection laws. Access to collated participant data will be restricted to appropriate research team staff. Computers used to collate the data will have restricted access. All data will be anonymised, and the master list will be kept as hard copy only in a locked filing cabinet in a locked office in a restricted-access university building. The database will be located in a dedicated trial storage space accessible by the research team only and which is backed up daily. No identifiable data will be stored electronically. No identifiable data will be transferred electronically or otherwise.

Discussion

Transforaminal epidural steroid injections are an effective treatment for spinal radicular pain. Although transforaminal epidural steroid injections are recommended as a first-line invasive treatment for sciatic pain,^{2,22} current clinical guidelines do not specify whether clinicians should take a supraneural or infraneural anatomical approach.

Anatomical studies and case reports have shown that the infraneural approach is associated with a lower risk of arterial damage, which can lead to spinal cord ischaemia and paralysis. Cases of paralysis after transforaminal epidural steroid

injections have been reported at every level of the lumbar spine, and T12 and S1, despite both CT and fluoroscopic guidance. Fourteen cases of paraplegia have been reported in the literature, but because there are no accurate records available regarding image-guided lumbar steroid injections, case reports may underestimate the true numbers of poor outcomes, so the rate of neurological complications is likely to be inaccurate.^{11–13,23}

The blood supply of the spinal cord and its nerve roots is via the posterior radicular arteries with marked anatomical inter-individual variability. The segmental feeders originate from the aorta through lumbar arteries to radiculomedullary arteries as anterior and posterior radicular arteries. The posterior radicular artery produces two longitudinal anastomotic channels within the canal, fed by its branches. The division and the location of these radicular arteries within the neural foramen vary.²⁴ At lumbar levels, arteries are seen more frequently in the upper part of the foramen than in the lower part of the foramen.²⁵ In a retrospective review of spinal angiograms, the primary segmental feeder, the artery of Adamkiewicz, was seen to be located in the upper half of the intervertebral foramen in 97% of cases.²⁶ The lumbar intervertebral veins also more commonly course through the upper part of the intervertebral foramen than the lower part of the foramen.²⁷ Thus, the needle trajectory through the upper part of the foramen is more likely to encounter the spinal vascular structures, linked to lack of efficacy of the block, epidural haematomas, and anterior spinal artery syndrome; this needle trajectory should be avoided.

The anatomical studies have delineated not only the existence of a peridural membrane, a connective tissue sheath that envelops the neural elements in the spinal canal, and neural foramen, but also their rich innervation, including the nociceptive fibres.^{28,29} These studies have identified a compartment in the caudal part of the intervertebral foramen bounded anteriorly by the disc and posteriorly by facet joints, where inflammatory mediators secondary to disc pathology can accumulate. This could be a potential target for interventions. Thus, the infraneural approach to transforaminal epidural injections would seem to be 'attractive' in theory to target the site of pathology.

Both the supraneural and infraneural approaches are widely used in the UK, although the supraneural is considered the standard technique. However, the infraneural approach avoids the radicular medullary artery, so the risk of catastrophic injury is removed. This trial will show whether the infraneural technique is not inferior to the supraneural approach and provide a basis for recommendations for clinical practice.

We plan to use a non-inferiority trial design, which aims to show that a treatment (in this case infraneural epidural) is not inferior to the standard technique (supraneural) and is either equally effective or better.^{15,16} If this can be established, infraneural can be recommended over supraneural, given the safety advantage that makes it preferable. The non-inferiority delta margin of 0.5 on the 0–10 NRS pain scale is considered exacting in chronic pain studies.

Dissemination plans and data sharing

Our results will be presented at relevant scientific meetings and published in a peer-reviewed journal. A report about the study will be posted on the Affa Sair website at the conclusion of the study. We also plan to disseminate results to clinical staff locally.

The datasets generated will be available upon reasonable request.

Authors' contributions

Funding application: HFG, SK, MOC.
Study protocol design: all authors.
Statistical input: MOC.
Drafting of paper: HFG.
Review/editing of paper: all authors.

Declarations of interest

HFG is a director and trustee of the *British Journal of Anaesthesia* and a member of the Editorial Board of *BJA Open*.

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