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Title Page

A Comparative Effectiveness Randomised Placebo Controlled Pilot Trial of the Management of Acute Lumbar Radicular Pain (SCIATICA)

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ABSTRACT

Introduction: Acute sciatica (symptom duration less than 4 weeks), a major cause of pain and disability, is a common presentation to medical practices and hospitals. Peri-neural steroid injection is often used with the hope of reducing pain and improving function in sciatic. More recently, there has been interest in using systemic corticosteroids in acute sciatica. However, there is limited evidence to inform effectiveness of perineural steroid in subacute and chronic sciatica and there is no evidence in acute sciatica, even though the practice is widespread. There is also limited evidence for the use of systemic corticosteroids in acute sciatica. Furthermore, the comparative effectiveness of perineural steroid versus systemic steroids has never been directly studied.

Methods and Analysis: SCIATICA is a single centre study of patients with acute sciatica designed to evaluate the feasibility of undertaking a 4-arm randomised controlled comparative effectiveness study of (i) CT-guided peri-neural steroid injection and (ii) systemic steroids (tapering dose over 15 days of oral dexamethasone) in a blinded randomised sham and placebo controlled trial. SCIATICA is designed to evaluate head-to-head, route versus pharmacology of corticosteroid intervention by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline, and includes additional full blinding with oral placebo and sham injection. The primary outcome measure is the Oswestry Disability Index (ODI) 3weeks post allocation of the intervention. Secondary outcome is the ODI at 48 weeks. Other outcomes include numerical rating scale for leg pain, Pain Detect Questionnaire, quality of life, medication use, need for rescue procedures or surgery, and adverse events. Results of outcomes from this RCT will be used to determine the sample size and power calculations for a full-scale study.

Ethics and dissemination: The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586). ClinicalTrials.Gov NCT03240783

STRENGTHS AND LIMITATION OF THIS STUDY

- This 4-arm trial evaluates the feasibility of undertaking a head-to-head route versus pharmacology of intervention randomised controlled trial by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline, AND includes additional full blinding with oral placebo and sham injection. Such a trial directly provides risk versus benefit of interventions of interest.
- Power calculations for a 4-arm comparative effectiveness fully blinded RCT will be established.
- Evaluates feasibility of recruiting and protocol adherence of patients from different settings: public hospital in-patients, emergency department presentation and general practitioner visits, in order to maximise generalisability of results.
- Evaluates the challenge of recruiting patients to a RCT where there often is an expectation of treatment benefit by health care professionals because of extrapolation of results from case series or RCTs with different inclusion criteria, but where there is no direct RCT evidence of benefit and risk in this patient population.
- Evaluates the challenge of recruiting patients to a RCT where there often is an expectation of treatment benefit by patients, family and friends by word-of-mouth or by searching the internet.
- Evaluates the adequacy and limitations of outcome measures in the acute sciatica, where pain, sensory and motor neurological symptoms all cause distress and disability, and where pain caused by nerve root irritation may often progress to loss of pain but is replaced by sensory loss or weakness from nerve root loss of conduction.

INTRODUCTION

The simple definition of sciatica is pain in the buttock and leg. The anatomic pathology is usually caused by lumbosacral disc herniation and degenerative lumbosacral spondylosis involving the L2/3 to L5/S1 intervertebral discs and foramina.[1] Sciatica can be associated with numbness, paraesthesia and weakness in the leg. The terms radicular pain and radiculopathy describe this neurological component of the pathology.[2] Sciatica and radicular pain is thought to arise from ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots from ischaemia or inflammation.[3] Radiculopathy indicates that there is conduction block of the spinal nerve or its roots from either mechanical compression or ischaemia from compromise of blood supply. Nonetheless, the terms are still used interchangeably and inconsistently in the randomised controlled trial (RCT) literature[4],[5], and in one recent review[5] 77% of all studies that used the term sciatica included participants with radicular pain and radiculopathy. This protocol uses the term sciatica to encompass sciatica, radicular pain and radiculopathy from lumbosacral nerve root pathology. The definition of acute sciatica in the RCT and systematic review literature differs. It has been defined as less than 4 weeks, less than 6 weeks and less than 12 weeks duration. Subacute sciatica is usually between 6-12 weeks duration. Chronic sciatica is greater than 12 weeks duration. In this protocol symptoms less than 4 weeks duration are defined as acute.

The prevalence of lumbosacral radiculopathy has been estimated at 3% to 5%[6], whereas referred leg pain is much higher.[4] In a inception cohort of 1,172 patients with acute low back pain presenting to primary care settings in Australia, 25% had leg pain[7]. The majority of participants (72%) with acute sciatica recover completely at by 12 months[7]. In another study, 50% of patients with acute sciatica recovered within 4 weeks. However, 30% had persistent leg pain and disability at 12 months[8].

Patients with acute sciatica are treated with a combination of paracetamol, opiate analgesia, non-steroidal anti-inflammatory drugs (NSAIDs), pregabalin, and physiotherapy although a systematic review of pharmacologic therapy that included NSAIDs, opioid analgesics, antidepressants, anticonvulsants, muscle relaxants, and opioid analgesics, showed no effect or only small effects in acute, subacute and chronic sciatica[9]. Neuropathic symptom modifiers such as pregabalin have also recently been shown to be ineffective[10].

Selective computed tomography fluoroscopic-guided transforaminal epidural injection of steroid with a local anaesthetic, also known as a spinal perineural injection, is increasingly being used in the management of patients with acute sciatica in hospital and community settings. For many medical practitioners this intervention is the expected treatment in patients who do not improve with conservative treatment if the CT or MRI findings support a diagnosis of a spinal nerve root compression that correlates with the clinical symptoms and signs. However, there is there is no RCT evidence to support the use of spinal perineural steroids in the acute sciatica. RCTs have required participants to have failed 6 weeks of conservative management prior to study recruitment because of the high spontaneous rate recovery. There are no Cochrane or systematic reviews on the management of acute sciatica with perineural steroid procedures[11]. The evidence for the use of spinal perineural injections in the acute setting is an extrapolation of relatively poor evidence in the subacute and chronic setting and the possibility that the procedure itself has a placebo effect.

During the 1970s, failure of conservative management in sciatica and the desire to avoid surgery led to the use of more invasive interventional procedures, such as epidural steroids. There are three approaches for epidural steroids: caudal, interlaminar and transforaminal. Evidence for the superiority of the transforaminal approach, which is the present-day approach, versus the other two is generally indirect[12] as there are few high quality head-to-head studies[13]. The transforaminal approach deposits steroid directly near the ventral epidural space at the affected unilateral nerve

root level. It is nowadays executed with CT fluoroscopic guidance, therefore is performed by interventional radiologists.

The first transforaminal approach RCT was published in 2000[14]. Since then five RCTs have been published[15][16][17][18][19]. These RCTs had low risk of bias from random sequence generation and participant and personnel blinding. All RCTs except one required a symptom duration of at least 4 weeks prior to recruitment. All but one RCT required MRI evidence of disc herniation[14] . Two studies excluded patients with evidence of foraminal stenosis[17][19]. Three studies did not report neurological features[16][18][19]. All studies included an epidural control, but only one study also included a non-epidural control[17]. Only two studies clearly specified the primary endpoint[17][18], but these two studies had incomplete follow-up as they did not obtain further data on patients who failed to achieve a 50% reduction of pain 4 weeks after the last procedure. In summary, none of the RCTs used CT-guided fluoroscopy as is the current practice. Where epidural saline was used as an epidural control, speculated mechanisms for effect include washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.

There have been over 60 reviews of epidural steroids in the last 15 years. Not surprisingly, given the heterogeneity of patient populations, interventions and study design and conduct differences, conclusions vary. A recent systematic review and meta-analysis [20] of transforaminal epidural steroids concludes that they provide "modest analgesic benefit at 3 months … but have no impact on disability". A meta-analysis that included all epidural steroid approaches (caudal, interlaminar and transforaminal)[12] concluded that the "small size of the treatment effects raises questions about the clinical utility of this procedure".

Harms have been reported with transforaminal epidural steroid injections[21] including infection and bleeding. In 2014, the Food and Drug Administration (FDA) issued a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including "loss of vision, stroke, paralysis, and death." [22]. The risk is greater for particulate versus non-particulate steroids and in cervical versus lumbosacral epidurals. Recently a consensus opinion paper was published on safeguards to prevent neurologic complications after epidural steroid injections[23]. The clinical considerations were based on conventional fluoroscopy with contrast and not with CT fluoroscopy. RCTs show no difference in efficacy between particulate and non-particulate steroids[24],[25],[26].

Unlike epidural steroids, systemic steroids have been studied in acute as well as subacute sciatica. A meta-analysis of 7 small of studies of variable quality of IM, IV and oral steroids found steroids were not superior to placebo and had more adverse events[27]. Adverse events, however, were clearly related to the very high dose of dexamethasone used in 3 of the 7 studies (120 mg of dexamethasone in 3 days which is the equivalent of 800mg of oral prednisone). In another systematic review[9] three studies of acute sciatica using smaller doses of steroid, a significant effect on short-term overall pain and leg pain was found. A RCT of IM steroid versus IM saline failed to show a difference in leg pain scores [17]. A blinded RCT reported that IV dexamethasone (8mg) improved pain scores at 24 hours and reduced ED length of stay compared to placebo. There was no difference at 6 weeks[28]. No CT/MRI imaging evidence was needed. A recent blinded RCT of patients with sciatica less than 12 weeks duration of oral prednisone (60mg 5 days, 40mg 5 days and 20mg 5 days) showed an improvement in function at 3 weeks and 52 weeks but no improvement in pain[29].

There is considerable support for perineural steroids for the management of acute sciatica in the medical community despite limited, direct, high quality research to inform effectiveness of CT-guided transforaminal epidural steroid in subacute and chronic sciatica and no evidence in the acute sciatica. Arguably, steroids may be more effective for sciatica when provided in the acute setting,

yet this treatment has not been subjected to rigorous evaluation. Other treatments for sciatica that are occasionally used in the acute setting are single high dose intramuscular or intravenous steroids, and a tapering course of oral steroids. Given their common use and perceived effectiveness, and the costs and potential harms associated with their use, there is an identified need to properly evaluate the use of epidural and systemic steroids in acute sciatica in adequately controlled trial designs with both a control arm for the route of procedure and a control arm for the pharmacology.

METHODS / ANALYSIS

Study Objectives

Primary objective

Undertake a pilot study of a sham and placebo parallel group randomised controlled trial of computed tomography (CT) fluoroscopic guided transforaminal lumbar epidural steroid versus oral steroid taper in patients with acute sciatica to evaluate the following issues: rate of recruitment, study conduct including randomisation allocation concealment, preparation of interventions, choice of procedural corticosteroid and local anaesthetic, blinding, efficient organisation of initial assessments, diagnostic imaging, and ensuring efficient study processes across hospital inpatient, emergency room/department presentation and general practice visits, and timeliness of providing the intervention within the 4 week acute sciatica requirement. Rate of recruitment is important particularly where there already is an expectation of treatment benefit by health care professionals because of extrapolation of results from case series or RCTs with different inclusion criteria, but where there is no direct RCT evidence of benefit and risk in this patient population. Rate of recruitment is also important because of the challenge of recruiting patients to a RCT where there already is an expectation of treatment benefit by patients, family and friends by word-of-mouth or by searching the internet, of the benefit of spinal perineural injections.

Secondary objectives

1. Obtain preliminary results from this RCT which will be used to calculate the sample size and power calculations for a full-scale study of treatments currently used in the management of acute lumbosacral radiculopathy of less than 4 weeks duration is the most effective in reducing pain and disability in the short-term and prevent progression to persistent or recurrent lumbosacral radiculopathy in the long term.
2. Evaluate the adequacy of outcome measures in acute sciatica, where pain, sensory and motor neurological symptoms all cause distress and disability, and where pain caused by nerve root irritation often progresses to loss of pain and may be replaced by sensory loss or weakness from nerve root conduction impairment. The importance of describing this multifactorial pathology and how it impacts the primary endpoint, the Oswestry Disability Index has substantive importance regarding the optimal primary and secondary endpoint for use in a main RCT. Other outcome measures will also be evaluated such as confounding by medication use and taper, protocol compliance and burden, confounding by modification of activities and need and timing of rescue procedures.
3. Although this is a feasibility study, for transparency the following are the pre-specified hypotheses for powering of a full-scale RCT; in patients with acute sciatica, CT/fluoroscopic guided transforaminal lumbar epidural steroid (spinal perineural injection of steroid) is (a) superior to sham injection and (b) equivalent to a 15 day tapering dose of oral dexamethasone in reducing short-term pain and disability (after 3 weeks) as determined by the Oswestry Disability Index.

Participants, interventions and outcomes

The study setting is the rheumatology service at a large teaching hospital in Sydney, Australia. The teaching hospital services a population of about 1 million of Southern Sydney. The eligibility criteria are as follows:

Inclusion criteria

(i) leg pain of any description with clinical findings consistent with single level radiculopathy,
(ii) minimum symptom duration > 72hrs,
(iii) maximum symptom duration < 3 weeks to ensure symptom duration at randomisation is < 4 weeks,
(iv) no previous episode of same level radicular pain in the previous 6 months,
(v) pain intensity at >30 on the Oswestry Disability Index (ODI),
(vi) imaging (MRI and/or CT) indicating herniated disc or foraminal stenosis or both, concordant with the level indicated by history and physical examination,
(vii) age at least 18 years

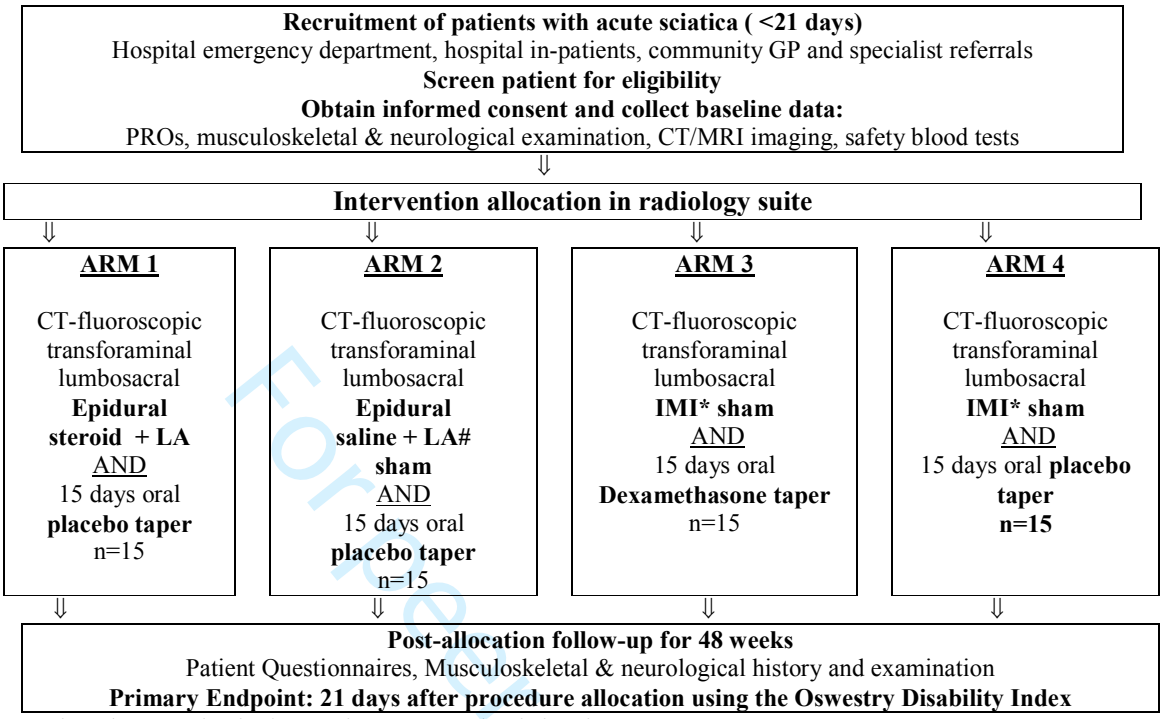
Exclusion criteria

(i) previous transforaminal epidural steroids at any level in the last 12 months,
(ii) previous oral steroids in the last 12 months,
(iii) any lumbar surgery at same level, or above or below the level at any time,
(iv) previous lumbar surgery at any other level to that in (iii) within the last 12 months,
(v) pregnancy, or lactation/breastfeeding
(vi) direct indication for neurosurgery (e.g. cauda equina syndrome, or progressive motor loss i.e. ≤ 3/5 power),
(vii) inability to read or understand English
(viii) any serious medical or psychiatric condition that may interfere with participation or outcome assessment such as: need for uninterrupted anti-coagulation, spinal fracture, active infection or metastatic disease suspected, active cancer, poorly controlled diabetes, or patients with diabetes on any insulin, uncontrolled hypertension (systolic blood pressure >180 or diastolic blood pressure >110 within 30 days of randomization date), active peptic ulcer disease, history of intolerance to steroid therapy, previous or current psychiatric history of bipolar disease, or secondary gain such as anticipated or ongoing legal proceedings, history of substance abuse
(ix) no other pathology likely to explain condition (e.g Guillain-Barre Syndrome, vasculitis)

Both MRI and CT scan are acceptable for entry criteria. If CT is equivocal regarding pathology or level, then the patient will proceed to MRI, or the patient is not included in the study. Scans are performed without contrast. All potential participants will be reviewed by a study physician (rheumatologist) who will undertake a history and physical general, musculoskeletal and neurological examination to ensure inclusion and exclusion criteria and exclude 'red flags' and alternate diagnoses. Full laboratory examination of efficacy and safety includes FBC, CRP, ESR, coagulation profile, electrolytes, urea, creatinine (EUC), liver function tests (LFTs), fasting blood glucose. Patients who can cease antiplatelet and anticoagulant medications safely will be given instructions on how to do so, or are excluded. The CT and/or MRI images are reported by an experienced radiologist who is unaware of the study, and the results are discussed with the participant and their treating physician. If the report is unclear, the images are reviewed by an independent radiologist at a radiology meeting to clarify imaging pathology. If imaging pathology remains unclear then eligibility is not met. The images are also reviewed by the interventional radiologist prior to the procedure (see Implementation). If the interventional radiologist cannot confirm the specified imaging pathology the procedure is aborted and the principal investigator is contacted.

Interventions

In the interventions are as follows and also described in Figure 1.



#LA=local anaesthetic *IMI=intramuscular injection

Figure 1.Study design and interventions

Arm 1. Selective CT/fluoroscopic guided transforaminal lumbar epidural steroid (1 ml) and local anaesthetic (1ml) injection AND oral placebo capsules (lactose) days 1-15, 8am and 6 pm.
Arm 2. Selective CT/fluoroscopic guided transforaminal lumbar epidural normal saline (0.9%) (1 ml) + local anaesthetic (1ml) injection AND oral placebo capsules (lactose) days 1-15, 8am and 6 pm.
Arm 3. Sham CT/fluoroscopic guided transforaminal lumbar sham injection which is needle placement down to muscle layer and no injection of any fluid AND oral dexamethasone capsules 15 day taper dosing - days 1-5 4 mg 8am and 6pm, days 6-10 2 mg 8am and 6pm days 11-15 1mg 8am and 6pm.
Arm 4. Sham CT/fluoroscopic guided transforaminal lumbar sham injection which is needle placement down to muscle layer and no injection of any fluid AND oral placebo capsules (lactose) days 1-15, 8am and 6 pm.

Procedural injectable intervention. In this study participants will receive dexamethasone 4mg (1ml) a non-particulate corticosteroid with the local anaesthetic lignocaine 1% (1ml) except if they are an inpatient at St George Hospital in which case participants will receive celestone chondrose 5.7mg/ml, (betamethasone) a particulate corticosteroid with the local anaesthetic bupivacaine 0.5% (1ml). This is at the direction of two interventional radiology investigators who have differing preferences regarding procedural agents. The interventional radiologist and their preference is known and will be addressed in the hierarchical linear model analysis. The normal saline epidural sham injection is 0.9% normal saline (1ml) and lignocaine 1% (1 ml) unless they are hospital inpatients in which case they will receive bupivacaine 0.5% as the local anaesthetic agent. The saline epidural sham provides the control for the procedure pharmacology. The IMI sham procedure is needle placement down to muscle layer and no injection of any fluid. The intervention is

performed by an experienced interventional radiologist. The intervention radiologist is not blind to the procedure (see section Blinding, for more information).

Oral intervention The oral steroid is dexamethasone. The 15 day taper dosing is days 1-5 4 mg 8am and 6pm, days 6-10 2 mg 8am and 6pm days 11-15 1mg 8am and 6pm. Dexamethasone has a longer biological half-life than prednisolone. The placebo is sucrose and lactose. The oral interventions are over-encapsulated in gelatine capsules packed with sucrose and lactose. Dexamethasone and placebo capsules have identical appearance and are prepared by a compounding pharmacist. The capsules are placed in three plastic bottles with clearly labelled instructions. At each telephone or in-person contact treatment adherence is monitored.

Concomitant management and interventions: All participants have concomitant therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. All concomitant therapy will be recorded at each visit. Rescue therapy includes perineural injection of steroid and neurosurgery.

Outcomes

A recent publication on core outcomes domains for clinical trials in non-specific low back pain recommended physical functioning, pain intensity, and health-related quality of life [30].

Primary outcome measure.

The Oswestry Disability Index (ODI) version 2.0 [31] is the primary outcome measure. The ODI is a functional status measure specifically developed for disorders of the spine and has been used in most RCTs of sciatica[32] and see Table 1. It is a 10-domain 2-page 5 minute questionnaire with ordered 6-response-item (0-5) scales for each question. The questions address domains of pain, physical functioning, sleeping, home/work functioning and impact on social life. The scores are summed, then doubled and the final score is 0-100. The ODI will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48. This will be administered at visits, phone or mail. The primary analysis is the short-term outcome, reduction of disability at 3 weeks on the ODI. The secondary analysis is the long-term outcome, reduction of disability at 48 weeks on the ODI.

Secondary outcomes.

Numerical Rating Scale (NRS) for leg pain is the main secondary outcome. A measure of leg pain is included in all studies of sciatica. The NRS is a validated [33] 11 point scale. Participants will be asked to rate their average leg pain over the preceding 24 hours. Zero represents 'no leg pain' and 10 represents 'worst imaginable pain'. Although the Visual Analogue Scale is a more frequently included measure, unlike the VAS, the NRS can be verbally administered by phone. This will be administered at Eligibility Baseline/Randomisation (day 0), day 1-7, weeks 2, 3, 6, 12, 24, 48.

Numerical Rating Scale (NRS) for back pain. The severity of back pain may differ to that of leg pain so both measures are needed. It is rated as an average over the preceding 24 hours and will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Pain DETECT Questionnaire [34]. At Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Short-Form 36 (SF-36) questionnaire [35] evaluates health related quality of life and will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48.

Lumbosacral and lower limb musculoskeletal and neurological history and clinical examination at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. This includes inspection of gait, lumbosacral spine and lower limbs for scoliosis, asymmetry, loss of lumbar lordosis, abnormal gait and stance, weakness, muscle wasting, muscle fasciculation, palpation of lumbosacral spine for tenderness and rigidity, movement of lumbosacral spine in flexion and extension, hip, knee and ankle range of movement, straight leg raise and femoral stretch test. Neurological examination of lower limb includes further inspection, examination for tone (normal, increased, decreased), clonus (present absent and beats of clonus if present), power (0, 1, 2, 3, 4, 4+ and 5 out of 5) for 12 lower limb movements (hip abduction, adduction, flexion, extension, knee flexion and extension, ankle dorsiflexion, plantar flexion, inversion and eversion, big toe extension and flexion) , knee and ankle reflexes (increased, normal, decreased absent), plantar reflexes (normal, up-going, equivocal, no response), and pinprick, light touch, proprioception and vibration sensory examination.

Work and health utilisation measures at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. These will include days missed from paid employment (if applicable) because of sciatica, use of health services such as doctor, other health-care provider related visits (acupuncture, chiropractic), injections and neurosurgical procedures.

Demographic and socioeconomic measures measured at baseline include age, gender, and occupation/previous occupation.

Imaging findings on CT and /or MRI will be used to define the site, level, type and degree of pathology using classification systems for disc herniation [36] and severity of nerve root compression [37]. This data will be used to determine imaging predictors of response.

Medications: use of all other medications including analgesics, NSAIDs, opiates, gabapentin and pregabalin will be documented at every visit.

Economic evaluation based on a cost-utility analysis in which the interventions are assess in terms of incremental costs per quality-adjusted-life-year using QALYs obtained from the **EuroQol 5D**[38]. The EuroQol questionnaire will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. Costs of the intervention will be assessed in terms of hospital, health care visits, investigations including additional CT/MRI imaging, procedure costs and medications costs. These will be valued with Diagnosis Related Groups cost weights, Medical Benefits Scheme standard fees, and Pharmaceutical Benefits Scheme. The perspective will be from the health sector. The incremental cost per QALY is estimated as the ratio of the difference in average cost and QALYs between intervention arms for three comparisons from: epidural steroid vs. dexamethasone taper vs. sham/placebo.

Adverse events will be collected at day 1, day 7, weeks 3, 6, 12, 24, 48. These will include steroid adverse effects (blood pressure, blood glucose, changes in mood and sleep) and procedural adverse effects (headaches, bleeding) and information about additional procedures, surgery and hospitalisations.

Table 1: Schedule of enrolment, interventions and assessments

	STUDY PERIOD											
	Screening& Eligibility	**Allocation**	**Post allocation**									**Close-out**
TIMEPOINT	-T1	0	T1	T2	T3		T4	T5	T6	T7	T8	T9
D=Day W=Week		**D0**	**D1**	**D 2-6**	**D7**	**D 8-15**	**D14**	**D21**	**W6**	**W12**	**W24**	**W48**
ENROLMENT												
Eligibility Screen	✓	✓										
Neurological and musculoskeletal Examination	✓	✓										
Safety Blood Tests	✓	✓	✓		✓			✓				
MRI (or CT if MRI contraindicated or CT clearly demonstrates imaging pathology)	✓											
Oswestry Disability Index	✓	✓										
Informed Consent	✓											
Allocation		✓										
INTERVENTIONS												
Procedural injection in radiology suite		X										
Oral medications		X	X	XXXX	X	XXXX XXXX						
ASSESSMENTS												
Outcome Variables												
Oswestry Disability Index	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Numerical Pain Rating Scales	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
PAIN DETECT Questionnaire	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
SF-36	✓	✓			✓		✓	✓	✓	✓	✓	✓
EQ-5D	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Work/health utilisation/costs	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Medication History	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Neurological and musculoskeletal Examination			✓		✓			✓	✓	✓	✓	✓
Safety Blood Tests			✓		✓							
Other Data variables												
Rescue procedure history			✓		✓			✓	✓	✓	✓	✓
Participation Randomization perception			✓		✓			✓	✓	✓	✓	✓
Adverse Events & Serious Adverse Event Assessment		✓	✓	✓	✓			✓	✓	✓	✓	✓

Sample size

Most trials of subacute and chronic sciatica of a peri-neural steroid injection have a sample size of 30 participants per arm. In this pilot our aim will be to recruit at least 15 participants per arm. This is a total of 60 participants. This is sufficient to evaluate feasibility and to determine sample size for a main study

Recruitment processes

Participants will be recruited from (i) EDs of public hospitals, (ii) current inpatients of public and private hospitals and (iii) referral from community general practitioner or medical specialist (rheumatologist, neurosurgeon or orthopaedic surgeon) from the Sydney metropolitan area around St George Hospital. It is anticipated that the majority of participants will be recruited from emergency department presentations and general practitioners. Participants with sciatica symptoms less than 21 days duration are screened so that participants can be evaluated and undergo the allocated intervention within the 4 weeks eligibility criteria.

St George Hospital Emergency Department, as well GPs and specialists in the hospital area have been provided information about SCIATICA study, the inclusion/exclusion criteria, explanation of the trial rationale, and the opening of a daily acute sciatica clinic at St George Hospital centre as the portal of entry for trial patients.

Participants presenting to the Emergency Department (ED) with acute sciatica are assessed according to ED's usual procedures and staff admit or discharge patients according to their usual care pathway. If the ED does not admit a potential acute sciatica participant, a study clinician is contacted by phone Monday-Friday 9am to 5pm (business hours) and a referral is faxed. Out of business hours, a referral is faxed to the acute sciatica clinic which is processed the next business day (see below). All referred participants are given a brochure by the referring ED clinician outlining the study. The acute sciatica clinic is also available for urgent referrals from community general practitioners and specialists. This is by fax or by telephone. These referred participants are also given a brochure by their referring clinician. All referred potential participants are logged. Within 1 to 3 days, Monday to Friday, all referred participants are contacted by telephone by a study clinician and a telephone history is obtained to ascertain suitability regarding inclusion and exclusion criteria. Where eligibility is clear or indeterminate, an eligibility visit is organised within the next couple of days. At this visit a full history and examination, musculoskeletal and neurological is conducted to determine underlying pathology, and if acute sciatica is likely, then lumbosacral imaging preferably with MRI imaging and blood pathology is requested. Patients complete routine clinical practice questionnaires as part of clinic audit including ODI, SF-36 and EQ-5D. Conservative therapy is initiated (medication/physiotherapy) as appropriate. Potential participants are provided with the Participant Information and Consent Form and further information regarding the RCT if eligibility criteria are likely. Once imaging and pathology becomes available the participant is contacted and informed of the results. If s/he meets the criteria s/he is invited to participate in the RCT. At one of the visits prior to randomisation, all participants are reviewed by the principal investigator to ensure that all eligibility criteria are met. This includes a full general, musculoskeletal and neurological history and clinical examination and confirmation of imaging. If eligibility criteria are met and the participant agrees to participate, then the participant proceeds down study pathway. Processes are in place to ensure that enrollees, if they agree to participate, are safely fast-tracked to randomisation and RCT interventions.

If patients do not agree to participate in the RCT they can either decide to continue their management in the acute sciatica clinic, and if their general practitioner is willing then the patient's ongoing management is determined by the rheumatologists who run the acute sciatica clinic. If the patient wishes to be managed by their GP, a letter from the acute sciatica clinic is sent to the GP to

facilitate management. The patient has the option of returning to the acute sciatica clinic for further management or advice as needed. A log of potential participants who decline or are ineligible for any reason is kept for later evaluation consistent with CONSORT guidelines. Reason for rejection or refusal will be recorded if available as well as age, gender, race/ethnicity and ODI score. If the participant does not wish to participate in the RCT but wish to be managed in the acute sciatica clinic they are included in a clinical audit of the management of acute sciatica. The management is determined in consultation with the patient and is generally conservative therapy unless there is severe pain and progressive functional disability preventing return to work or normal activities, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

The participant may clearly not meet the eligibility criteria at telephone screening. If patient safety is not an urgent consideration, patients who have anticipated or ongoing legal proceedings, need uninterrupted anti-coagulation or active cancer (as exclusion criteria) are not progressed to the eligibility visit but are asked to see or return to their treating doctor. Participants that do not have any leg pain are also asked to see or return to their treating doctor. However, if a referred patient has a history that suggests cauda equina syndrome or symptoms suggestive of malignant or infection-related pathology, the patient is seen urgently in the acute sciatica clinic and appropriate investigations and management are instituted.

If the participant does not wish to participate they are included in a clinical audit of the management of acute sciatica during the admission and the participant is continued to be managed according to the treating clinician. This is generally conservative therapy unless there is progressive severe pain and functional disability preventing discharge, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

If the participant is admitted to hospital with acute sciatica the admitting team will contact the study investigators. Most patients with acute sciatica in our setting are either admitted under the general medical team, the rheumatology team or the neurosurgical team. The same processes are followed for in-patients as described above for out-patient referrals. Only a study investigator can consent a participant to participate in SCIATICA

All participants are told that participation is voluntary, they can discuss participation with family, friends or their health care practitioners, and if they decide not to participate, it will not affect the treatment they receive now or in the future. They can have family and friends with them during the consent process. They can also withdraw from the study once it has started, at any time without having to give a reason.

Assignment of interventions

Sequentially numbered, opaque and sealed envelopes contain the randomised intervention. Participants are randomly allocated 1:1:1:1 by computer-generated random numbers using permuted blocks stratified by duration of sciatica (≤2 weeks, >2 weeks). The randomisation schedule including details of blocking schedule are held off-site by the randomised allocation sequence study investigator who is not involved in participant recruitment , assignment of interventions or data collection to ensure allocation concealment. This study investigator places the study medications and procedure instructions for each arm in separate opaque sealed envelopes. These two envelopes in turn are placed into a single larger opaque sealed envelope labelled with a sequential number and the randomisation number. The sealed envelopes are held in a locked cabinet until retrieved by the blinded study investigators who are involved in participant recruitment, provision of the study interventions, participant management and data collection. The acute sciatica clinic study investigators are blind to the study intervention.

Implementation of interventions

The day of study intervention implementation, the participant has safety bloods performed, unless eligibility safety bloods had occurred in the previous week. The participant completes the study questionnaires and the study clinician once more ascertains eligibility criteria by history and examination immediately in the morning before attending the radiology suite. If the criteria are still met the study clinician indicates the exact site of the perineural injection on a request form that is provided to the interventional radiologist. For example, "perform a perineural injection of corticosteroid and local anaesthetic at L5/S1 targeting the right S1 nerve root". The MRI images are also provided to the interventional radiologist. The research officer retrieves the next in sequence numbered large opaque labelled sealed envelope. The research officer accompanies the participant, taking the interventional request, images (films or on CD) and large opaque labelled sealed envelope to the radiology suite. At the radiology suite the research officer opens sealed opaque envelope, gives the 'procedure' envelope with instructions to the radiologist and exits. The radiologist evaluates the MRI images, then opens the procedure envelope. It contains one of three instructions: (i) perineural steroid and local anaesthetic injection, (ii) perineural normal saline and local anaesthetic injection or (iii) intramuscular sham injection down to muscle layer but no injection of any fluid. The side (right or left) and lumbosacral level (e.g L5/S1) is determined by the radiology request form. The participant is positioned prone as per a perineural injection, the CT fluoroscope is positioned as if a perineural injection is performed, local anaesthetic is injected into the skin and subcutaneous tissue. Radiologist and his staff maintain patient blinding. CT/fluoroscopic guided transforaminal lumbar epidural radiation parameters are set to reduce radiation dose. There is no radiation dose for CT/fluoroscopic guided transforaminal lumbar sham injection because the parameters are set to zero although the machine is on. All CT fluoroscopy images are saved for further analysis.

At the end of the procedure once outside the CT fluoroscopy room, the research officer gives the opaque envelope marked "Dexamethasone or placebo capsules" to the participant and explains how the medications are to be taken over the next 15 days. There are three plastic bottles labelled Days 1-5, Days 6-10 and Days 11-15. The participant opens the Day 1 labelled bottle and swallows the capsule. The participant continues to lie flat for at least one hour after the procedure, the participant is forbidden to drive for 24 hours and a person accompanies them home. The interventional radiology procedure report states that the participant had a procedure as part of the SCIATICA RCT and to contact the chief investigator if there is a concern, a phone number is provided.

Masking/Blinding.

All personnel except the radiologist delivering the procedure and the investigator responsible for randomisation will be blind to the randomisation arm. The trial participant, study clinicians, research officers, participant's treating care providers, outcome assessors, and data analysts are blind to the intervention assignments. In the event of a serious medical emergency during which the treating doctor must know in which arm the participant was randomised, the randomised code can be broken. Each participant is given a 24 hour emergency contact number and the principal investigator contacts the investigator who holds the randomisation schedule to determine the participants allocated intervention.

Data collection, management and analysis

Data collection methods

Data quality of outcome, baseline and other trial data is safeguarded with standardisation, assessor training and duplication of measurements and assessments by research officers administering the questionnaires and study clinicians undertaking the history and clinical examinations. All assessments are reviewed and the history and clinical findings confirmed by the principal investigator prior final eligibility determination. Study clinicians meet every 2 weeks to discuss ongoing assessments, issues of standardisation, equivocal or unclear findings and or any other concerns. All questionnaire data is scanned, with range checks for data values, and verified. Free

text data scanned and verified. Clinical data is coded and verified. Participants' retention and complete follow-up is encouraged through contact by phone or text and visits are organised so that they are maximally convenient for participants. This often requires visits to be conducted at the end of the normal working day.

Data analysis Plan

Although this is a pilot study to evaluate several important clinical and trial design considerations the following data analysis plan is proposed for transparency. Effectiveness of treatment is analysed by intention-to-treat and the data analyst will be blind to group allocation. A two-tailed p-value <0.05 is considered statistical significant. The primary analysis is an analysis of variance evaluating the effects of treatment on the ODI at week 3, using treatment arm, baseline ODI and duration of symptoms in days as covariates. There are a total of 6 comparisons in this pilot RCT. *The primary comparison is Arm 1 versus Arm 4, i.e. epidural steroid versus sham procedure.* However, similar analyses will be applied to the other treatment comparisons (i.e. epidural steroid versus epidural saline, epidural steroid versus oral dexamethasone, oral dexamethasone versus oral placebo, epidural saline versus oral dexamethasone, epidural saline versus sham procedure). No penalty will be applied for the multiple comparisons in this pilot RCT. All comparisons are made at Day 21, where Day 0 is the day of the procedural intervention immediately followed by the first dose of the oral intervention. Day 21 is the 3 week endpoint. Similar analyses will also be applied at the 6 and 48 week endpoints for the ODI. Multilevel linear mixed model will examine time trend by treatment group interaction. This linear mixed model will be used to model ODI trajectory across all 10 time-points by treatment group, where treatment group is a property of the persons and visit is nested within person. The random-effects portion of the model specifies that months are a random effect. Analyses will be undertaken unadjusted and adjusted for medication use and other covariates. There is no interim analysis.

Other outcome measures (NRSs, SF-36, EQ-5D and clinical data measured on a continuous scale will also be analysed with multilevel mixed effects linear regression. All analyses will be undertaken unadjusted and adjusted for other medication use, type of procedural steroid, presence of neurological signs, and MRI findings with multivariate methods. A full description of neurological signs will be reported in tabular form and descriptive statistics. Safety data will be analysed in reported in tabular form and with descriptive statistics.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee and is guided by a Data Safety and Monitoring Board and South Eastern Sydney Local Health District Human Research Ethics Executive (HREC15/331) Protocol version 3, 67 April 2016. Any changes to the protocol are reported to this committee.

Data monitoring

A data safety and monitoring committee (DSMC) will meet after the first 10 participants have been randomised to evaluate study conduct and safety. The DSMC will consist of the principal investigator (non-voting), a interventional radiologist, neurosurgeon, rheumatologist, and general physician. Adverse event monitoring and withdrawal of participants are discussed. The DSMC will meet every 4 months. The DSMC will be provided blinded data but unblinded data can be provided for a specific participant if requested by the committee. If requested it will be provided by an investigator who holds the randomisation schedule.

Harms

CT/fluoroscopic guided transforaminal lumbar epidural steroid (1 ml) and local anaesthetic (1ml) is used in the management of sciatica of all durations. The risks associated with this procedure include:

Dural puncture: the needle penetrates into the sac encasing the nerves within the spinal canal, causing leakage of fluid contained within the sac, known as CSF (cerebrospinal fluid). The risk of this procedure is approximately 1% and is treated with flat bed rest for four hours.

Infection: most of these are minor (1-2%), however can be serious (<0.1%) requiring hospital admission, intravenous antibiotics and surgery.

Bleeding: this is rare although more common in patients with bleeding disorders and on "blood thinning" medication. Patients who cannot cease their medications will be excluded from the study (e.g. patients with mechanical heart valve, recent deep venous thrombosis and pulmonary embolus, recent cardiac stent). Otherwise, patients on warfarin have an INR and depending on the value will be asked to cease the warfarin 5 days prior to the procedure and an INR will be checked the day before the procedure and the value must be <1.5. Pradaxa (dabigatran) must be ceased 3 days prior to the procedure, aspirin and platelet inhibitors (plavix, iscover, ticlopidine, persantin) ceased 7 days prior to the procedure, cleaxane cease 24 hours prior to the procedure. NSAIDs and COX2 inhibitors do not need to be ceased.

Nerve damage: from direct needle trauma, or as a consequence of the above mentioned complications is rare.

Stroke and spinal cord injury: Most of the reported serious complications result from inadvertently injecting steroids with particulate matter into blood vessels close to the injection site, which can lead to brain or spinal cord injury. The risk of stroke or spinal cord damage from a transforaminal epidural steroid injection in the back is quite low when done under CT fluoroscopy.

The risks of high dose short term oral corticosteroids are more common (10-20%) and include insomnia, nervousness, increased appetite, indigestion, headache. There are risks in patients with active peptic ulcer disease of perforation, worsening hypertension in patients with severe hypertension, and hyperglycemia in patients with poorly controlled diabetes or on insulin treatment. These patients are excluded from the trial. Patients who are on diet or oral hypoglycemic medications will be monitored with blood tests to minimise risk of significant hyperglycemia. However, these symptoms and abnormal blood tests will cease with stopping of treatment. There is no risk of suddenly stopping dexamethasone in this study as it is only being administered for 2 weeks.

It is important that women participating in this study are not pregnant or lactating as the study CT scan fluoroscopy radiation, although small, is not zero, and dexamethasone is secreted in breast milk.

An adverse event is any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable or unintended sign, symptom or condition and/or an observation that may or may not be related to the study treatment. A serious adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital/birth defect, condition requiring unnecessary medical or surgical intervention. Solicited reporting of adverse events occurs Days 1 to 7, Weeks 3, 6, 12, 24, 48. Participants can also contact study investigators at any time if they have any concerns. All adverse events are reported to the principal investigator and all serious adverse events are reported to the DMSC and Human Research Ethics Committee.

Auditing

A study meeting to audit trial conduct occurs fortnightly. There is no independent trial audit other than that provided by the DSMC and that required by the Human Research Ethics Committee.

DISCUSSION

Clinical, trial design and political significance

There is no randomised controlled trial evidence for the use of CT-guided transforaminal epidural steroid in acute sciatica. There is limited evidence for the use of oral steroids in acute and subacute sciatica. There is a clear advantage of directly comparing different interventions in a single randomised control trial. These advantages include improving internal validity, marginally reducing sample size, and limiting heterogeneity by standardising assessments and conduct procedures. However, there are also disadvantages such as longer time to trial recruitment, therefore longer time to trial completion, more exclusion criteria because of differing interventions, and difficulty explaining design to participants. Often evidence is based on incremental advances in large simple 2-arm studies. Other discussion issues additional to those specific to the study objectives include advantages and disadvantages of different trial considerations in the management of acute sciatica, particularly if comparing a procedural intervention with oral medications, the effectiveness of blinding, when to offer rescue therapy, the difficulty recruiting participants to a randomised controlled trial when non-evidence based therapy based is delivered because new treatments have face validity and a considerable placebo effect.

Access to Data and Dissemination

The investigators have access to the final trial dataset. There are no contractual agreements limiting access. Study results of this trial will be submitted for publication in a peer-reviewed journal. Individual level data will be made available after the findings of the study have been published. This data can be used for IPD meta-analyses or for further exploratory research. To obtain this data please contact Marissa Lassere.
The trial is registered on ClinicalTrials. Gov - NCT03240783

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COMPETING INTERESTS STATEMENT

There are no competing interests.

AUTHORS' CONTRIBUTION

Marissa Lassere conceived and designed the study. Marissa Lassere and Kent Johnson wrote the first draft of the protocol. Peter Smerdely, Grant Pickard and Jeanette Thom critically reviewed the protocol for important intellectual content and approved the final version.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17, 18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5, 7-8
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 13, 14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In HREC protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	approved
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11,12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	IN HREC protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In patient consent/HREC documentation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	None used
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	HREC
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

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Randomised Placebo Controlled Pilot/Feasibility Trial of the Management of Acute Sciatica (SCIATICA).

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Title Page

Randomised Placebo Controlled Pilot/Feasibility Trial of the Management of Acute Sciatica (SCIATICA).

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ABSTRACT

Introduction: Acute sciatica (symptom duration less than 4 weeks), a major cause of pain and disability, is a common presentation to medical practices and hospital emergency departments. Selective computed tomography (CT) fluoroscopy transforaminal epidural steroid injection (TESI) is often used with the hope of reducing pain and improving function. Recently, there has been interest in using systemic corticosteroids in acute sciatica. However, there is limited evidence to inform efficacy of selective CT fluoroscopy transforaminal epidural steroid in subacute and chronic sciatica and there is no evidence in acute sciatica, even though the practice is widespread. There is also limited evidence for the use of systemic corticosteroids in acute sciatica. Furthermore, the efficacy of selective CT fluoroscopy transforaminal epidural steroid versus systemic steroids has never been directly studied.

Methods and Analysis: SCIATICA is a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of undertaking a blinded 4-arm randomised controlled intervention study of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of interventions. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. Secondary outcome is the ODI at 48 weeks. Other outcomes include numerical rating scale for leg pain, Pain Detect Questionnaire, quality of life, medication use, rescue procedures or surgery, and adverse events. Results of outcomes from this RCT will be used to determine the feasibility, sample size and power calculations for a large multicenter study.

Ethics and dissemination: The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586). ClinicalTrials.Gov NCT03240783

STRENGTHS AND LIMITATION OF THIS STUDY

- In the setting of acute sciatica (less than 4 weeks duration), this 4-arm trial evaluates the feasibility of undertaking a head-to-head route versus pharmacology of intervention randomised controlled trial by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline, and includes blinding with both oral placebo and sham injection across each arm. Such a trial directly provides risk versus benefit of interventions of interest.
- Evaluates feasibility of recruiting and protocol adherence of participants from different referral and demographic settings: public hospital inpatients, private hospital inpatients, emergency department presentations and general practitioner visits.
- Evaluates the challenge of recruiting participants to a RCT of acute sciatica where there often is an expectation of treatment benefit of a procedural intervention by health care professionals (and patients given frequent use of the internet for health care advice), because of a large placebo effect, the natural history of the condition, and extrapolation of results from case series or RCTs with different inclusion criteria, but where there is no direct RCT evidence of benefit and risk .

INTRODUCTION

The colloquial definition of sciatica is pain in the buttock and leg and it is a term understood by the nonprofessional population. The anatomic pathology is usually caused by lumbosacral disc herniation and degenerative lumbosacral spondylosis involving the L2/3 to L5/S1 intervertebral discs and foramina.[1] Therefore sciatica can be associated with numbness, paraesthesia and weakness in the leg. The terms radicular pain and radiculopathy describe this neurological component of the pathology by health-care professionals and researchers.[2] Radicular pain is thought to arise from ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots from ischaemia or inflammation.[3] Radiculopathy indicates that there is conduction block of the spinal nerve or its roots from either mechanical compression or ischaemia. Nonetheless, the terms are still used interchangeably and inconsistently in the randomised controlled trial (RCT) literature.[4],[5] This study defines the term sciatica as radicular pain with or without radiculopathy from lumbosacral nerve root pathology. The definition of acute sciatica in the RCT and systematic review literature also differs. It has been defined as less than 4 weeks, less than 6 weeks and less than 12 weeks duration. Subacute sciatica is usually between 6-12 weeks duration. Chronic sciatica is greater than 12 weeks duration. In this protocol symptoms less than 4 weeks duration are defined as acute.

The prevalence of lumbosacral radiculopathy has been estimated at 3% to 5%[6], whereas referred leg pain is much higher.[4] In an inception cohort of 1,172 patients with acute low back pain presenting to primary care settings in Australia, 25% had leg pain[7]. The majority of participants (72%) with acute sciatica recover completely by 12 months[7]. In another study, 50% of patients with acute sciatica recovered within 4 weeks. However, 30% had persistent leg pain and disability at 12 months[8].

Patients with acute sciatica are treated with a combination of paracetamol, opiate analgesia, non-steroidal anti-inflammatory drugs (NSAIDs)[9-11] pregabalin, and physiotherapy although a systematic review of pharmacologic therapy that included NSAIDs, opioid analgesics, antidepressants, anticonvulsants, muscle relaxants, and opioid analgesics, showed no effect or only small effects in acute, subacute and chronic sciatica[12]. Neuropathic symptom modifiers such as pregabalin have also recently been shown to be ineffective[13].

During the 1970s, failure of conservative management in sciatica and the desire to avoid surgery led to interventional procedures, including epidural steroid injections (ESI). There are three approaches for epidural steroid injections: caudal, interlaminar and transforaminal. The transforaminal approach deposits steroid directly near the ventral epidural space at the affected unilateral nerve root level. Evidence for the superiority of the selective transforaminal approach versus the caudal and interlaminar is generally indirect[14] as there are few high quality head-to-head studies[15]. Selective fluoroscopy (with or without computed tomography (CT) guided fluoroscopy) transforaminal epidural steroid injection (TESI) with local anaesthetic, colloquially described as a "spinal perineural steroid injection", is increasingly being used in the management of patients with acute sciatica in hospital and community settings in the absence of any RCTs undertaken to evaluate the benefit of this procedure in patients with acute sciatica. There are no Cochrane reviews on the management of acute sciatica with epidural steroids of any route[16]. In reviews of epidural steroid injections (caudal, laminar or transforaminal) in sciatica of any duration, not surprisingly, given the heterogeneity of patient populations, interventions, study design and study conduct, conclusions vary considerably. Two recent meta-analyses of epidural steroids in subacute and chronic sciatica [17],[14] conclude that treatment effects are small and of only short duration.

The first transforaminal approach RCT was published in 2000[18]. Five RCTs have been published[19-23] that have had low risk of bias from random sequence generation and participant and personnel blinding. These RCTs show considerable heterogeneity in study design. All RCTs

except one required a symptom duration of at least 4 weeks prior to recruitment. No RCT used CT fluoroscopy. All but one RCT required magnetic resonance imaging (MRI) evidence of disc herniation[18] . Two studies excluded patients with evidence of foraminal stenosis [21 23]. Three studies did not report neurological features.[20],[22],[23] All studies included an epidural control, but only one study also included a non-epidural control[21]. Only two studies clearly specified the primary endpoint[21],[22], but these two studies had incomplete follow-up as they did not obtain further data on patients who failed to achieve a 50% reduction of pain 4 weeks after the last procedure. Where epidural saline was used as an epidural control, speculated mechanisms for a therapeutic effect include washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.[21],

Harms have been reported with transforaminal epidural steroid injections[24] including infection and bleeding. In 2014, the Food and Drug Administration (FDA) issued a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including "loss of vision, stroke, paralysis, and death." [25]. The risk is greater for particulate versus non-particulate steroids and in cervical versus lumbosacral epidurals. Recently a consensus opinion paper was published on safeguards to prevent neurologic complications after epidural steroid injections[26]. The clinical considerations were based on conventional fluoroscopy with contrast and not with CT fluoroscopy. RCTs show no difference in efficacy between particulate and non-particulate steroids[27-29].

Unlike epidural steroids, systemic steroids have been studied in acute as well as subacute sciatica. A meta-analysis of 7 small of studies of variable quality of intramuscular (IM), intravenous (IV) and oral steroids found steroids were not superior to placebo and had more adverse events[30]. Adverse events, however, were clearly related to the very high dose of dexamethasone used in 3 of the 7 studies (120 mg of dexamethasone in 3 days which is the equivalent of 800mg of oral prednisone). In another systematic review[12] three studies of acute sciatica using smaller doses of steroid, a significant effect on short-term overall pain and leg pain was found. A RCT of IM steroid versus IM saline failed to show a difference in leg pain scores[21]. A blinded RCT reported that IV dexamethasone (8mg) improved pain scores at 24 hours and reduced ED length of stay compared to placebo. There was no difference at 6 weeks[31]. No CT/MRI imaging evidence was required. A recent blinded RCT of patients of oral steroids (prednisone 60mg 5 days, 40mg 5 days and 20mg 5 days) with sciatica less than 12 weeks duration showed an improvement in function at 3 weeks and 52 weeks but no improvement in pain[32].

In summary, there are two issues that are relevant that provides the rationale for this pilot/feasibility study (i) the condition under study i.e. acute, subacute or chronic sciatica, (ii) the route of interventional procedure (caudal, interlaminar and fluoroscopic transforaminal epidural (the last with or without CT guidance) or systemic route. There are no RCTs in acute sciatica published using steroid epidurals of any type. There are RCTs in acute sciatica with systemic steroids. In subacute and chronic sciatica there are no RCTs that have used selective CT fluoroscopy transformational steroid injection, indicative of the fast pace of changing technological procedural interventions without RCT evidence. Arguably, steroids may be more effective for sciatica when provided in the acute setting, but this should be subjected to rigorous evaluation. In Australia selective transforaminal epidural steroids is guided by computed tomography (CT) fluoroscopy, therefore is performed by interventional radiologists. Given their use and perceived effectiveness, and the costs and potential harms associated with their use, there is an identified need to properly evaluate the use of epidural and systemic steroids in acute sciatica in adequately controlled trial designs with a control arm for the route of procedure. Furthermore, given that there is a rationale for the benefit of epidural saline in acute sciatica, epidural steroid could be directly compared to epidural saline to evaluate pharmacology versus a simple physical washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.

There is a clear advantage of directly comparing different interventions in a single randomised control trial. These advantages include improving internal validity, marginally reducing sample size, and limiting heterogeneity by standardising assessments and conduct procedures. However, there are also disadvantages such as longer time to trial recruitment, therefore longer time to trial completion, more exclusion criteria because of differing interventions, and difficulty explaining design to participants.

METHODS / ANALYSIS

Study Objectives

Primary objective

Undertake a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of a blinded 4-arm RCT of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days of a tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of corticosteroid intervention by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline and includes blinding with oral placebo and sham injection across all arms. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. The primary analysis is comparison of CT fluoroscopy guided transforaminal lumbar epidural steroid versus sham injection (Arm 1 versus Arm 4 in Figure 1. Study Design).

The pilot/feasibility study will evaluate the following issues: rate of recruitment, study conduct including randomisation allocation concealment, preparation of interventions, choice of procedural corticosteroid and local anaesthetic, blinding, efficient organisation of initial assessments, diagnostic imaging, and ensuring efficient study processes across public/private hospital inpatients, emergency department /room (ED/R) presentations and general practice visits, and timeliness of providing the intervention within the 4 week acute sciatica requirement. Rate of recruitment is important particularly where there already is an expectation of treatment benefit “spinal perineural steroid injections” by health care professionals and patients.

This pilot/ feasibility study is a single centre Human Research Ethics Committee (HREC) study, but includes recruitment from multiple sources and the interventions will be delivered in public hospital, private hospital and community radiology practices. The recruitment of participants and the delivery of the interventions have been designed to identify feasibility issues given these different settings.

Secondary objectives

1. Obtain preliminary results from this RCT which will be used to calculate the sample size and power calculations for a full-scale study of treatments currently used in the management of acute lumbosacral radiculopathy of less than 4 weeks duration is the most effective in reducing pain and disability in the short-term and prevent progression to persistent or recurrent lumbosacral radiculopathy in the long term.
2. Evaluate the adequacy of outcome measures in acute sciatica, where pain, sensory and motor neurological symptoms all cause distress and disability, and where pain caused by nerve root irritation often progresses to loss of pain and may be replaced by sensory loss or weakness from nerve root conduction impairment. The importance of describing this multifactorial pathology and how it impacts the primary endpoint, the Oswestry Disability Index has substantive importance regarding the optimal primary and secondary endpoint for use in a full-scale RCT. Other outcome measures will also be evaluated such as confounding by medication use and taper, protocol compliance and burden, confounding by modification of activities and need and timing of rescue procedures.

3. Although this is a feasibility study, for transparency the following are the pre-specified hypotheses for powering a full-scale RCT. In patients with acute sciatica, selective CT fluoroscopy transforaminal lumbar epidural steroid (Arm 1) is (a) superior to control (Arm 4) and (b) non-inferior to a 15 day tapering dose of oral dexamethasone (Arm 3) in reducing short-term pain and disability (after 3 weeks) as determined by the Oswestry Disability Index. Further information regarding hypotheses and sample size is described in the sample size section.

Participants, interventions and outcomes

The study setting is the rheumatology service at a large teaching hospital in Sydney, Australia. The teaching hospital services a population of about 1 million of Southern Sydney. The eligibility criteria are as follows:

Inclusion criteria

(i) leg pain of any description with clinical findings consistent with single level radiculopathy,
(ii) minimum symptom duration > 72hrs,
(iii) maximum symptom duration < 3 weeks to ensure symptom duration at randomisation is < 4 weeks,
(iv) no previous episode of same level radicular pain in the previous 6 months,
(v) pain intensity at >30 on the Oswestry Disability Index (ODI),
(vi) imaging (MRI and/or CT) indicating herniated disc or foraminal stenosis or both, concordant with the level indicated by history and physical examination,
(vii) age at least 18 years

Exclusion criteria

(i) previous transforaminal epidural steroids at any level in the last 12 months,
(ii) previous oral steroids in the last 12 months,
(iii) any lumbar surgery at same level, or above or below the level at any time,
(iv) previous lumbar surgery at any other level to that in (iii) within the last 12 months,
(v) pregnancy, or lactation/breastfeeding
(vi) direct indication for neurosurgery (e.g. cauda equina syndrome, or progressive motor loss i.e. ≤ 3/5 power),
(vii) inability to read or understand English
(viii) any serious medical or psychiatric condition that may interfere with participation or outcome assessment such as: need for uninterrupted anti-coagulation, spinal fracture, active infection or metastatic disease suspected, active cancer, poorly controlled diabetes, or patients with diabetes on any insulin, uncontrolled hypertension (systolic blood pressure >180 or diastolic blood pressure >110 within 30 days of randomization date), active peptic ulcer disease, history of intolerance to steroid therapy, previous or current psychiatric history of bipolar disease, or secondary gain such as anticipated or ongoing legal proceedings, history of substance abuse
(ix) no other pathology likely to explain condition (e.g Guillain-Barre Syndrome, vasculitis)

Both MRI and CT scan are acceptable for entry criteria. If CT is equivocal regarding pathology or level, then the patient will proceed to MRI, or the patient is not included in the study. Scans are performed without contrast. All potential participants will be reviewed by a study physician (rheumatologist) who will undertake a history and physical general, musculoskeletal and neurological examination to ensure inclusion and exclusion criteria and exclude 'red flags' and alternate diagnoses. Full laboratory examination of efficacy and safety includes full blood count (FBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), coagulation profile, electrolytes, urea, creatinine (EUC), liver function tests (LFTs), fasting blood glucose. Patients who

can cease antiplatelet and anticoagulant medications safely will be given instructions on how to do so, or are excluded. The CT and/or MRI images are reported by an experienced radiologist who is unaware of the study, and the results are discussed with the participant and their treating physician. If the report is unclear, the images are reviewed by an independent radiologist at a radiology meeting to clarify imaging pathology. If imaging pathology remains unclear then eligibility is not met. The images are also reviewed by the interventional radiologist prior to the procedure (see Implementation). If the interventional radiologist cannot confirm the specified imaging pathology the procedure is aborted and the principal investigator is contacted.

Interventions

The interventions are as follows and also summarised in Table 1 and Figure 1.

Procedural interventions. Once the specific spinal nerve pathology has been selected clinically and on imaging (e.g. right S1 nerve root at L5/S1 intervertebral space), all participants are given an injection of local anaesthetic (lignocaine or bupivacaine) into the skin and subcutaneous tissue at this selected site.

Participants in Arm 1 will receive selective CT fluoroscopy transforaminal epidural dexamethasone 4mg (1ml) a non-particulate corticosteroid with the local anaesthetic lignocaine 1% (1ml). However, if participants are an inpatient at St George Hospital they will receive betamethasone (1ml) as celestone chondrose 5.7mg/ml, a particulate corticosteroid with the local anaesthetic bupivacaine 0.5% (1ml). This is at the direction of two interventional radiology investigators who have differing preferences regarding procedural agents. The interventional radiologist and their preference is known and will be addressed in the hierarchical linear model analysis.

Participants in Arm 2 will receive selective CT fluoroscopy transforaminal epidural 0.9% normal saline (1ml) and lignocaine 1% (1 ml) unless they are hospital inpatients in which case they will receive bupivacaine 0.5% as the local anaesthetic agent. The saline epidural has two purposes in this pilot/feasibility study. There is no consensus in the literature regarding the optimal control for the evaluation of epidural steroids [33]. Moreover, there is some evidence that it has a therapeutic effect[21]. Therefore this pilot/feasibility study is designed to explore these issues by including both epidural saline arm (Arm 2) and a sham injection (Arms 3 and 4).

Participants in Arms 3 and Arms 4 will receive sham selective CT fluoroscopy intramuscular injection with needle placement down to muscle layer and no injection of any fluid. The intervention is performed by an experienced interventional radiologist. The intervention radiologist is not blind to the procedure (see section Blinding, for more information).

Oral intervention. The oral steroid is dexamethasone. The 15 day taper dosing is (i) 4 mg at 8am and 6pm days 1-5, (ii) 2 mg 8am and 6pm days 6-10, and (iii) 1mg 8am and 6pm days 11-15. Dexamethasone has a longer biological half-life than prednisolone. The oral interventions are over-encapsulated in gelatine capsules packed with sucrose and lactose. The placebo is sucrose and lactose only. Participants in Arm 3 receive the oral dexamethasone capsules, and participants in Arms 1, 2 and 4 receive the placebo capsules. Dexamethasone and placebo capsules have identical appearance and are prepared by a compounding pharmacist. The capsules are placed in three plastic bottles with clearly labelled instructions. At each telephone or in-person contact treatment adherence is monitored.

Concomitant management and interventions: All participants have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. All concomitant therapy will be recorded at each visit. Rescue therapy includes CT fluoroscopy transforaminal epidural of steroid and neurosurgery.

Table 1: Summary of the experimental interventions by Arm

Arm	Experimental intervention
Arm 1 **Intervention 1** Injectable Dexamethasone and Lignocaine OR Betamethasone and Bupivacaine selective CT fluoroscopy guided transforaminal lumbar epidural steroid	**Drug: Betamethasone OR Dexamethasone Injectable** Procedural agents. The steroid and local anaesthetic preparation is determined by interventional radiologist's preferences regarding the use of particulate or non-particulate steroids. Dexamethasone 4mg (1ml) is a non-particulate corticosteroid and is used with the local anaesthetic lignocaine 1% (1ml). Betamethasone Sodium Phosphate/Acetate 5.7 mg/ml Injectable is a particulate corticosteroid and is used with the local anaesthetic bupivacaine 0.5% (1ml). Other Name: celestone chondrase 5.7 mg/ml injectable suspension Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 2 **Intervention 2** Normal Saline Flush, 0.9% Injectable Solution with either Bupivacaine or Lignocaine selective CT fluoroscopy guided transforaminal lumbar epidural normal saline	**Drug: Normal Saline Flush, 0.9% Injectable Solution** Procedural agents. The local anaesthetic preparation used with the Normal Saline Flush, 0.9% Injectable Solution, will be standardized to replicate current radiology interventional practices: either local anaesthetic bupivacaine 0.5% (1ml) or local anaesthetic lignocaine 1% (1ml). Other: Sham injection and/or oral placebo The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 3 **Intervention 3** Dexamethasone oral capsule 15 day tapered dosing as follows: (i) days 1-5, 4 mg morning and evening, (ii) days 6-10, 2 mg morning and evening, and (iii) days 11-15, 1mg morning and evening.	**Drug: Dexamethasone Oral Tablet** Dexamethasone Oral Tablet: 15 day taper dosing is: days 1-5 8mg (4mg morning and evening) , days 6-10 4 mg (2mg morning and evening), and days 11-15 2 mg (1mg morning and evening). The dexamethasone is over-encapsulated in a gelatine capsule that is identical to the placebo capsule in appearance. Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 4 **Control** Sham injection and/or oral placebo: CT/ fluoroscopy guided (parameters set to zero) transforaminal lumbar sham (needle placement down to muscle and no injection of any fluid) AND placebo oral tablets taper.	**Sham Injection and/or oral placebo** The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.

Outcomes

A recent publication on core outcomes domains for clinical trials in non-specific low back pain recommended physical functioning, pain intensity, and health-related quality of life [34].

Primary outcome measure.

The Oswestry Disability Index (ODI) version 2.0 [35] is the primary outcome measure. The ODI is a functional status measure specifically developed for disorders of the spine and has been used in most RCTs of sciatica[36] and see Table 2. It is a 10-domain 2-page 5 minute questionnaire with ordered 6-response-item (0-5) scales for each question. The questions address domains of pain, physical functioning, sleeping, home/work functioning and impact on social life. The scores are summed, then doubled and the final score is 0-100. The ODI will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48. This will be administered at visits, phone or mail. The primary analysis is the short-term outcome, reduction of disability at 3 weeks on the ODI. The secondary analysis is the long-term outcome, reduction of disability at 48 weeks on the ODI.

Secondary outcomes.

Numerical Rating Scale (NRS) for leg pain is the main secondary outcome. A measure of leg pain is included in all studies of sciatica. The NRS is a validated[37] 11 point scale. Participants will be asked to rate their average leg pain over the preceding 24 hours. Zero represents 'no leg pain' and 10 represents 'worst imaginable pain'. Although the Visual Analogue Scale (VAS) is a more frequently included measure, unlike the VAS, the NRS can be verbally administered by phone. This will be administered at Eligibility Baseline/Randomisation (day 0), day 1-7, weeks 2, 3, 6, 12, 24, 48.

Numerical Rating Scale (NRS) for back pain. The severity of back pain may differ to that of leg pain so both measures are needed. It is rated as an average over the preceding 24 hours and will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Pain DETECT Questionnaire [38]. At Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Short-Form 36 (SF-36) questionnaire [39] evaluates health related quality of life and will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48.

Lumbosacral and lower limb musculoskeletal and neurological history and clinical examination at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. This includes inspection of gait, lumbosacral spine and lower limbs for scoliosis, asymmetry, loss of lumbar lordosis, abnormal gait and stance, weakness, muscle wasting, muscle fasciculation, palpation of lumbosacral spine for tenderness and rigidity, movement of lumbosacral spine in flexion and extension, hip, knee and ankle range of movement, straight leg raise and femoral stretch test. Neurological examination of lower limb includes further inspection, examination for tone (normal, increased, decreased), clonus (present absent and beats of clonus if present), power (0, 1, 2, 3, 4, 4+ and 5 out of 5) for 12 lower limb movements (hip abduction, adduction, flexion, extension, knee flexion and extension, ankle dorsiflexion, plantar flexion, inversion and eversion, big toe extension and flexion) , knee and ankle reflexes (increased, normal, decreased absent), plantar reflexes (normal, up-going, equivocal, no response), and pinprick, light touch, proprioception and vibration sensory examination.

Work and health utilisation measures at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. These will include days missed from paid employment (if applicable) because of sciatica, use of health services such as doctor, other health-care provider related visits (e.g. acupuncture, chiropractic), injection procedures and neurosurgery. This information will be obtained by interview at each visit and is documented in the case report form developed for the study.

Demographic and socioeconomic measures measured at baseline include age, gender, and occupation/previous occupation.

Imaging findings on CT and /or MRI will be used to define the site, level, type and degree of pathology using classification systems for disc herniation [40] and severity of nerve root compression [41]. This data will be used to determine imaging predictors of response.
Medications: use of all other medications including analgesics, NSAIDs, opiates, gabapentin and pregabalin will be documented at every visit.

Economic evaluation: Outcomes for an economic evaluation will also be collected in this feasibility study. A cost-effectiveness analysis will be undertaken using the ODI and a cost-utility analysis [42] using the EQ5D-5L for incremental costs per quality-adjusted-life-year (QALY)[43]. The EQ5D-5L questionnaire will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. Work and health utilisation measures described above will also be collected. Costs within each randomised arm will be assessed in terms of hospital, health care visits, investigations, such as CT and MRI imaging, procedure costs and medications costs. These direct costs are determined with Diagnosis Related Groups cost weights for hospital in-patients, and for outpatients by the Australian Medical Benefits Scheme standard fees, and the Australian Pharmaceutical Benefits Scheme (PBS). These costs are determined by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) Manual of Resources items and their associated costs used for economic analyses[44], [45]. The PBAC does not require questionnaires of productivity[44],[45] such as the PRODISQ[46] and similar questionnaires of resource utilization.[47]
Adverse events will be collected at day 1, day 7, weeks 3, 6, 12, 24, 48. These will include steroid adverse effects (blood pressure, blood glucose, changes in mood and sleep) and procedural adverse effects (headaches, bleeding) and information about additional procedures, surgery and hospitalisations.

Table 2: Schedule of enrolment, interventions and assessments

	STUDY PERIOD											
	Screening& Eligibility	**Allocation**	**Post allocation**									**Close-out**
TIMEPOINT	-T1	0	T1	T2	T3		T4	T5	T6	T7	T8	T9
D=Day W=Week		**D0**	**D1**	**D 2-6**	**D7**	**D 8-15**	**D14**	**D21**	**W6**	**W12**	**W24**	**W48**
ENROLMENT												
Eligibility Screen	✓	✓										
Neurological and musculoskeletal Examination	✓	✓										
Safety Blood Tests	✓	✓	✓		✓			✓				
MRI (or CT if MRI contraindicated or CT clearly demonstrates imaging pathology)	✓											
Oswestry Disability Index	✓	✓										
Informed Consent	✓											
Allocation		✓										
INTERVENTIONS												
Procedural injection in radiology suite		X										
Oral medications		X	X	XXXX	X	XXXX XXXX						
ASSESSMENTS												
Outcome Variables												
Oswestry Disability Index	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Numerical Pain Rating Scales	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
PAIN DETECT Questionnaire	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
SF-36	✓	✓			✓		✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Work/health utilisation/costs	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Medication History	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Neurological and musculoskeletal Examination			✓		✓			✓	✓	✓	✓	✓
Safety Blood Tests			✓		✓							
Other Data variables												
Rescue procedure history			✓		✓			✓	✓	✓	✓	✓
Participation Randomization perception			✓		✓			✓	✓	✓	✓	✓
Adverse Events & Serious Adverse Event Assessment		✓	✓	✓	✓			✓	✓	✓	✓	✓

Sample size

Most trials of subacute and chronic sciatica of a selective CT fluoroscopy transforaminal epidural steroid injection have a sample size of 30 participants per arm. The primary outcome in this pilot/feasibility study is the ODI at 3 weeks comparing epidural steroid and sham injection (Arm 1 vs. Arm 4). With 15 participants per arm, there is 85% power to detect a difference of 17 ODI points between these two arms, given a standard deviation of change of ODI of 15.1 points[32]. Statistical test on which calculation is based is the independent two-sample t-test with a two-tailed alpha of 0.05 (Stata 14). This is a total of 60 participants in this pilot/feasibility study. This is sufficient to evaluate feasibility of the study design, study conduct and determine sample size for a full-scale multicentre study. However, this ODI difference is a large unrealistic effect. The minimum clinically important difference in ODI scores in one study was 7.0 points [48], and an international consensus group found empirical evidence of 4 to 15 ODI points[49] and recommended a cutoff value of 10 ODI points. Given that we are recruiting participants with acute sciatica of less than 4 weeks duration, an ODI difference of at least 10 ODI points is very reasonable. A sample size of 49 participants per arm will provide 90% power to detect a minimum clinically important difference of 10 ODI points assuming a standard deviation of 15.1 with a two-tailed alpha of 0.05 (Stata 14). Allowing for 20% dropout (which at 3 weeks is unlikely but at 48 weeks is more likely), 236 participants will be recruited, 59 to each arm. Although there are 6 possible comparisons in a 4 arm trial, controlling for type-1 error rate is not needed when several different experimental arms are compared with the control[50],[51]. Therefore no multiplicity adjustment is needed for: (i) Comparison I- Arm 1 versus Arm 4 (epidural steroid is superior to control), (ii) Comparison II - Arm 2 versus Arm 4 (epidural saline is superior to control), and Comparison III - Arm 3 versus Arm 4 (oral steroid is superior to control). However, in order to proceed to Comparison IV, Arm 1 versus Arm 3 (epidural steroid is superior to oral steroids), we must first demonstrate that Comparisons I and III were statistical significant, and there must be a type-1 error consideration[52]. Furthermore, if the hypothesis is that oral steroid is non-inferior to epidural steroids, then the ignorable difference must also be prespecified. The pilot/feasibility study will provide data that will be helpful in determining these sample size calculations. The feasibility study will be informative regarding the estimated mean difference in this population, its standard deviation, and pattern of missing data at each of the study visits.

Recruitment processes

Participants will be recruited from (i) Emergency departments (EDs) of public hospitals, (ii) current inpatients of public and private hospitals and (iii) referral from community general practitioner or medical specialist (rheumatologist, neurosurgeon or orthopaedic surgeon) from the Sydney metropolitan area around St George Hospital. It is anticipated that the majority of participants will be recruited from emergency department presentations and general practitioners. Participants with sciatica symptoms less than 21 days duration are screened so that participants can be evaluated and undergo the allocated intervention within the 4 weeks eligibility criteria.

St George Hospital Emergency Department, as well GPs and relevant specialists in the geographic area (population approximately 270,000) serviced by this hospital area have been provided information about SCIATICA study, the inclusion/exclusion criteria, explanation of the trial rationale, and the opening of a daily acute sciatica clinic at St George Hospital centre as the portal of entry for trial patients.

Participants presenting to the Emergency Department (ED) with acute sciatica are assessed according to ED's usual procedures and staff admit or discharge patients according to their usual care pathway. If the ED does not admit a potential acute sciatica participant, a study clinician is contacted by phone Monday-Friday 9am to 5pm (business hours) and a referral is faxed. Out of business hours, a referral is faxed to the acute sciatica clinic which is processed the next business

day (see below). All referred participants are given a brochure by the referring ED clinician outlining the study. The acute sciatica clinic is also available for urgent referrals from community general practitioners and specialists. This is by fax or by telephone. These referred participants are also given a brochure by their referring clinician. All referred potential participants are logged. Within 1 to 3 days, Monday to Friday, all referred participants are contacted by telephone by a study clinician and a telephone history is obtained to ascertain suitability regarding inclusion and exclusion criteria. Where eligibility is clear or indeterminate, an eligibility visit is organised within the next couple of days. At this visit a full history and examination, musculoskeletal and neurological is conducted to determine underlying pathology, and if acute sciatica is likely, then lumbosacral imaging preferably with MRI imaging and blood pathology is requested. Patients complete routine clinical practice questionnaires as part of clinic audit including ODI, SF-36 and EQ-5D-5L. Conservative therapy is initiated (medication/physiotherapy) as appropriate. Potential participants are provided with the Participant Information and Consent Form and further information regarding the RCT if eligibility criteria are likely. Once imaging and pathology becomes available the participant is contacted and informed of the results. If s/he meets the criteria s/he is invited to participate in the RCT. At one of the visits prior to randomisation, all participants are reviewed by the principal investigator to ensure that all eligibility criteria are met. This includes a full general, musculoskeletal and neurological history and clinical examination and confirmation of imaging. If eligibility criteria are met and the participant agrees to participate, then the participant proceeds down study pathway. Processes are in place to ensure that enrolees, if they agree to participate, are safely fast-tracked to randomisation and RCT interventions.

If patients do not agree to participate in the RCT they can either decide to continue their management in the acute sciatica clinic, and if their general practitioner is willing then the patient's ongoing management is determined by the rheumatologists who run the acute sciatica clinic. If the patient wishes to be managed by their GP, a letter from the acute sciatica clinic is sent to the GP to facilitate management. The patient has the option of returning to the acute sciatica clinic for further management or advice as needed. A log of potential participants who decline or are ineligible for any reason is kept for later evaluation consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines[53]. Reason for rejection or refusal will be recorded if available as well as age, gender, race/ethnicity and ODI score. If the participant does not wish to participate in the RCT but wish to be managed in the acute sciatica clinic they are included in a clinical audit of the management of acute sciatica. The management is determined in consultation with the patient and is generally conservative therapy unless there is severe pain and progressive functional disability preventing return to work or normal activities, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

The participant may clearly not meet the eligibility criteria at telephone screening. If patient safety is not an urgent consideration, patients who have anticipated or ongoing legal proceedings, need uninterrupted anti-coagulation or active cancer (as exclusion criteria) are not progressed to the eligibility visit but are asked to see or return to their treating doctor. Participants that do not have any leg pain are also asked to see or return to their treating doctor. However, if a referred patient has a history that suggests cauda equina syndrome or symptoms suggestive of malignant or infection-related pathology, the patient is seen urgently in the acute sciatica clinic and appropriate investigations and management are instituted.

If the participant does not wish to participate they are included in a clinical audit of the management of acute sciatica during the admission and the participant is continued to be managed according to the treating clinician. This is generally conservative therapy unless there is progressive severe pain and functional disability preventing discharge, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

If the participant is admitted to hospital with acute sciatica the admitting team will contact the study investigators. Most patients with acute sciatica in our setting are either admitted under the general medical team, the rheumatology team or the neurosurgical team. The same processes are followed for in-patients as described above for out-patient referrals. Only a study investigator can consent a participant to participate in SCIATICA

All participants are told that participation is voluntary, they can discuss participation with family, friends or their health care practitioners, and if they decide not to participate, it will not affect the treatment they receive now or in the future. They can have family and friends with them during the consent process. They can also withdraw from the study once it has started, at any time without having to give a reason.

Assignment of interventions

Sequentially numbered, opaque and sealed envelopes contain the randomised intervention. Participants are randomly allocated 1:1:1:1 by computer-generated random numbers using permuted blocks stratified by duration of sciatica (≤2 weeks, >2 weeks). The randomisation schedule including details of blocking schedule are held off-site by the randomised allocation sequence study investigator who is not involved in participant recruitment , assignment of interventions or data collection to ensure allocation concealment. This study investigator places the study medications and procedure instructions for each arm in separate opaque sealed envelopes. These two envelopes in turn are placed into a single larger opaque sealed envelope labelled with a sequential number and the randomisation number. The sealed envelopes are held in a locked cabinet until retrieved by the blinded study investigators who are involved in participant recruitment, provision of the study interventions, participant management and data collection. The acute sciatica clinic study investigators are blind to the study intervention.

Implementation of interventions

The day of study intervention implementation, the participant has safety bloods performed, unless eligibility safety bloods had occurred in the previous week. The participant completes the study questionnaires and the study clinician once more ascertains eligibility criteria by history and examination immediately in the morning before attending the radiology suite. If the criteria are still met the study clinician indicates the exact site of the CT fluoroscopy transforaminal epidural on a request form that is provided to the interventional radiologist. For example, “perform a selective CT fluoroscopy transforaminal epidural of corticosteroid and local anaesthetic at L5/S1 targeting the right S1 nerve root”. The MRI images are also provided to the interventional radiologist. The research officer retrieves the next in sequence numbered large opaque labelled sealed envelope. The research officer accompanies the participant, taking the interventional request, images (films or on CD) and large opaque labelled sealed envelope to the radiology suite. At the radiology suite the research officer opens sealed opaque envelope, gives the ‘procedure’ envelope with instructions to the radiologist and exits. The radiologist evaluates the MRI images, then opens the procedure envelope. It contains one of three instructions: (i) selective CT fluoroscopy transforaminal epidural steroid and local anaesthetic injection, (ii) selective CT fluoroscopy transforaminal epidural normal saline and local anaesthetic injection or (iii) intramuscular sham injection down to muscle layer but no injection of any fluid. The side (right or left) and lumbosacral level (e.g L5/S1) is determined by the radiology request form. The participant is positioned prone as per a CT fluoroscopy transforaminal epidural, the CT fluoroscope is positioned as if a CT fluoroscopy transforaminal epidural is performed, local anaesthetic is injected into the skin and subcutaneous tissue. Radiologist and his staff maintain patient blinding. CT/fluoroscopy guided transforaminal lumbar epidural radiation parameters are set to reduce radiation dose. There is no radiation dose for CT/fluoroscopy guided transforaminal lumbar sham injection because the parameters are set to zero although the machine is on. All CT fluoroscopy images are saved for further analysis.

At the end of the procedure once outside the CT fluoroscopy room, the research officer gives the opaque envelope marked "Dexamethasone or placebo capsules" to the participant and explains how the medications are to be taken over the next 15 days. There are three plastic bottles labelled Days 1-5, Days 6-10 and Days 11-15. The participant opens the Day 1 labelled bottle and swallows the capsule. The participant continues to lie flat for at least one hour after the procedure, the participant is forbidden to drive for 24 hours and a person accompanies them home. The interventional radiology procedure report states that the participant had a procedure as part of the SCIATICA RCT and to contact the chief investigator if there is a concern, a phone number is provided.

Masking/Blinding.
All personnel except the radiologist delivering the procedure and the investigator responsible for randomisation and preparing the interventions will be blind to the randomisation arm. The trial participant, study clinicians, research officers, participant's treating care providers, outcome assessors, and data analysts are blind to the intervention assignments. In the event of a serious medical emergency during which the treating doctor must know in which arm the participant was randomised, the randomised code can be broken. Each participant is given a 24 hour emergency contact number and the principal investigator contacts the investigator who holds the randomisation schedule to determine the participants allocated intervention.

Data collection, management and analysis
Data collection methods
Data quality of outcome, baseline and other trial data is safeguarded with standardisation, assessor training and duplication of measurements and assessments by research officers administering the questionnaires and study clinicians undertaking the history and clinical examinations. All assessments are reviewed and the history and clinical findings confirmed by the principal investigator prior final eligibility determination. Study clinicians meet every 2 weeks to discuss ongoing assessments, issues of standardisation, equivocal or unclear findings and or any other concerns. All questionnaire data is scanned, with range checks for data values, and verified. Free text data scanned and verified. Clinical data is coded and verified. Participants' retention and complete follow-up is encouraged through contact by phone or text and visits are organised so that they are maximally convenient for participants. This often requires visits to be conducted at the end of the normal working day.

Data/Statistical Analysis Plan
Although this is a pilot/feasibility study to evaluate several important clinical and trial design considerations the following data analysis plan is proposed for transparency. Efficacy of treatment is analysed by intention-to-treat and the data analyst will be blind to arm allocation. A two-tailed p-value <0.05 is considered statistical significant. The primary analysis is an analysis of variance evaluating the effects of treatment on the ODI at week 3, using treatment arm, baseline ODI and duration of symptoms in days as covariates. The primary comparison is epidural steroid versus control. However, similar analyses will be applied to the other treatment comparisons with control (epidural saline versus control, oral steroid versus control) without a type-1 error penalty. However, the epidural steroid versus oral steroid comparison will require type-1 error consideration[52]. All comparisons are made at Day 21, where Day 0 is the day of the procedural intervention immediately followed by the first dose of the oral intervention. Day 21 is the 3 week endpoint.

Similar analyses will also be applied at the 6 and 48 week endpoints for the ODI. Multilevel linear mixed model will examine time trend by treatment arm interaction. This linear mixed model will be used to model ODI trajectory across all 10 time-points by treatment arm, where treatment arm is a property of the persons and visit is nested within person. The random-effects portion of the model specifies that months are a random effect. Analyses will be undertaken unadjusted and adjusted for medication use and other covariates. Missing data will be handled with multiple imputation, using

iterative Markov chain Monte Carlo (MCMC) which requires the assumption that the data are missing at random[54]. An intention to treat analysis with multiple imputation is the primary analysis, however, a completers analysis will also be undertaken as a secondary analysis. The value of undertaking a feasibility study is that patterns and reasons of missing data that are not at random may be identified and in the full-scale study targeted efforts made to reduce this potential bias. There is no interim analysis.

Other outcome measures (NRSs, SF-36, EQ-5D and clinical data measured on a continuous scale) will also be analysed with multilevel mixed effects linear regression. All analyses will be undertaken unadjusted and adjusted for other medication use, type of procedural steroid, presence of neurological signs, and MRI findings with multivariate methods. A full description of neurological signs will be reported in tabular form and descriptive statistics. Safety data will be analysed in reported in tabular form and with descriptive statistics.

Economic Evaluation

This feasibility study will provide data to identify issues conducting an economic evaluation for the full-scale study. The rationale for undertaking an economic evaluation is to evaluate the feasibility of undertaking a pre-specified cost-effectiveness economic evaluation in the full-scale study. In Australia, all drugs and more recently, certain procedures, undergo a cost-effectiveness analysis to determine whether they will be subsidised by the Australian government. This is usually performed from the perspective of the health-care sector rather than from the societal perspective[44]. We will be following these guidelines. In this pilot/feasibility study we will ascertain the feasibility of obtaining the outcome (including QALYs) and cost data in a valid manner, determine how much outcome and cost data are missing, and obtain estimates of mean and standard deviation of outcomes and costs. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[42] statement checklist will also be followed to report the economic evaluation component in the full study.

In this pilot/feasibility study all participants in all study arms have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. *Arm 4, the control arm, therefore is the usual care arm.* In this pilot/feasibility study the perspective of the health sector is undertaken using intention-to-treat. The incremental cost per ODI or QALY (based on EQ5D-L) will be estimated as the ratio of the difference in average cost and ODI or QALY between intervention arms for three comparisons: (i) epidural steroid vs. control, (ii) oral steroid vs. control, and (iii) epidural steroid vs. oral steroid. Missing data will be imputed with iterative Markov chain Monte Carlo methods. Sensitivity analyses will be performed by converting the SF-36 to SF-6D QALYs to compare QALYs, as well as other sensitivity analyses as recommended by CHEERS.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee and is guided by a Data Safety and Monitoring Board and South Eastern Sydney Local Health District Human Research Ethics Executive (HREC15/331) Protocol version 3, 67 April 2016. Any changes to the protocol are reported to this committee.

Data monitoring

A data safety and monitoring committee (DSMC) will meet after the first 10 participants have been randomised to evaluate study conduct and safety. The DSMC will consist of the principal investigator (non-voting), a interventional radiologist, neurosurgeon, rheumatologist, and general physician. Adverse event monitoring and withdrawal of participants are discussed. The DSMC will

meet every 4 months. The DSMC will be provided blinded data but unblinded data can be provided for a specific participant if requested by the committee. If requested it will be provided by an investigator who holds the randomisation schedule.

Harms

CT fluoroscopy guided transforaminal lumbar epidural steroid (1 ml) and local anaesthetic (1ml) is used in the management of sciatica of all durations. The risks associated with this procedure include:

Dural puncture: the needle penetrates into the sac encasing the nerves within the spinal canal, causing leakage of fluid contained within the sac, known as CSF (cerebrospinal fluid). The risk of this procedure is approximately 1% and is treated with flat bed rest for four hours.

Infection: most of these are minor (1-2%), however can be serious (<0.1%) requiring hospital admission, intravenous antibiotics and surgery.

Bleeding: this is rare although more common in patients with bleeding disorders and on "blood thinning" medication. Patients who cannot cease their medications will be excluded from the study (e.g. patients with mechanical heart valve, recent deep venous thrombosis and pulmonary embolus, recent cardiac stent). Otherwise, patients on warfarin have an INR and depending on the value will be asked to cease the warfarin 5 days prior to the procedure and an INR will be checked the day before the procedure and the value must be <1.5. Pradaxa (dabigatran) must be ceased 3 days prior to the procedure, aspirin and platelet inhibitors (plavix, iscover, ticlopidine, persantin) ceased 7 days prior to the procedure, clexane cease 24 hours prior to the procedure. NSAIDs and COX2 inhibitors do not need to be ceased.

Nerve damage: from direct needle trauma, or as a consequence of the above mentioned complications is rare.

Stroke and spinal cord injury: Most of the reported serious complications result from inadvertently injecting steroids with particulate matter into blood vessels close to the injection site, which can lead to brain or spinal cord injury. The risk of stroke or spinal cord damage from a transforaminal epidural steroid injection in the back is quite low when done under CT fluoroscopy.

The risks of high dose short term oral corticosteroids are more common (10-20%) and include insomnia, nervousness, increased appetite, indigestion, headache. There are risks in patients with active peptic ulcer disease of perforation, worsening hypertension in patients with severe hypertension, and hyperglycemia in patients with poorly controlled diabetes or on insulin treatment. These patients are excluded from the trial. Patients who are on diet or oral hypoglycemic medications will be monitored with blood tests to minimise risk of significant hyperglycemia. However, these symptoms and abnormal blood tests will cease with stopping of treatment. There is no risk of suddenly stopping dexamethasone in this study as it is only being administered for 2 weeks.

It is important that women participating in this study are not pregnant or lactating as the study CT scan fluoroscopy radiation, although small, is not zero, and dexamethasone is secreted in breast milk.

An adverse event is any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable or unintended sign, symptom or condition and/or an observation that may or may not be related to the study treatment. A serious adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital/birth defect, condition requiring unnecessary medical or surgical intervention. Solicited reporting of adverse events occurs Days 1 to 7, Weeks 3, 6, 12, 24, 48. Participants can also contact study investigators

at any time if they have any concerns. All adverse events are reported to the principal investigator and all serious adverse events are reported to the DMSC and Human Research Ethics Committee.

Auditing
A study meeting to audit trial conduct occurs fortnightly. There is no independent trial audit other than that provided by the DSMC and that required by the Human Research Ethics Committee.

Access to Data and Dissemination
The investigators have access to the final trial dataset. There are no contractual agreements limiting access. Study results of this trial will be submitted for publication in a peer-reviewed journal. Individual level data will be made available after the findings of the study have been published. This data can be used for IPD meta-analyses or for further exploratory research. To obtain this data please contact Marissa Lassere.
The trial is registered on ClinicalTrials. Gov - NCT03240783

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COMPETING INTERESTS STATEMENT
There are no competing interests.

AUTHORS' CONTRIBUTION
Marissa Lassere conceived and designed the study. Marissa Lassere and Kent Johnson wrote the first draft of the protocol. Peter Smerdely, Grant Pickard and Jeanette Thom critically reviewed the protocol for important intellectual content and approved the final version.

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FIGURE LEGEND

Figure 1. Study Flow Chart

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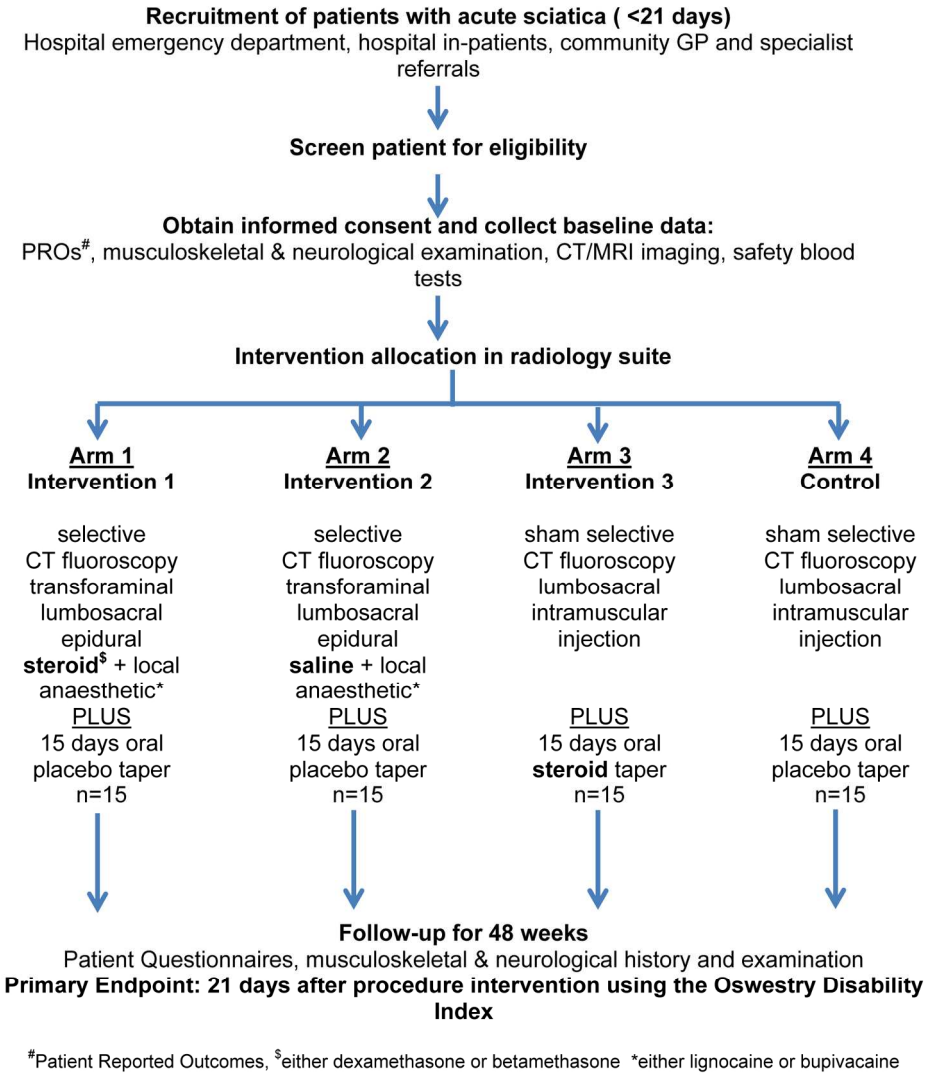

Figure 1. Study Flow Chart

171x184mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4, 7-8
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12,13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17,18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10,11,15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In HREC protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	approved
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	IN HREC protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In patient consent/HREC documentation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	None used
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	HREC
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

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Randomised Placebo Controlled Pilot Trial of the Management of Acute Sciatica (SCIATICA): A Feasibility Study

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Title Page

Randomised Placebo Controlled Pilot Trial of the Management of Acute Sciatica (SCIATICA): A Feasibility Study

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ABSTRACT

Introduction: Acute sciatica (symptom duration less than 4 weeks), a major cause of pain and disability, is a common presentation to medical practices and hospital emergency departments. Selective computed tomography (CT) fluoroscopy transforaminal epidural steroid injection (TESI) is often used with the hope of reducing pain and improving function. Recently, there has been interest in using systemic corticosteroids in acute sciatica. However, there is limited evidence to inform management of selective CT fluoroscopy transforaminal epidural steroid in subacute and chronic sciatica and there is no evidence in acute sciatica, even though the practice is widespread. There is also limited evidence for the use of systemic corticosteroids in acute sciatica. Furthermore, the management of selective CT fluoroscopy transforaminal epidural steroid versus systemic steroids has never been directly studied.

Methods and Analysis: SCIATICA is a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of undertaking a blinded 4-arm randomised controlled intervention study of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of interventions. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. Secondary outcome is the ODI at 48 weeks. Other outcomes include numerical rating scale for leg pain, Pain Detect Questionnaire, quality of life, medication use, rescue procedures or surgery, and adverse events. Results of outcomes from this RCT will be used to determine the feasibility, sample size and power calculations for a large multicenter study.

Ethics and dissemination: The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586). ClinicalTrials.Gov NCT03240783

STRENGTHS AND LIMITATION OF THIS STUDY

- In the setting of acute sciatica (less than 4 weeks duration), this 4-arm trial evaluates the feasibility of undertaking a head-to-head route versus pharmacology of intervention randomised controlled trial by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline, and includes blinding with both oral placebo and sham injection across each arm. Such a trial directly provides risk versus benefit of interventions of interest.
- Evaluates feasibility of recruiting and protocol adherence of participants from different referral and demographic settings: public hospital inpatients, private hospital inpatients, emergency department presentations and general practitioner visits.
- Evaluates the challenge of recruiting participants to a RCT of acute sciatica where there often is an expectation of treatment benefit of a procedural intervention by health care professionals (and patients given frequent use of the internet for health care advice), because of a large placebo effect, the natural history of the condition, and extrapolation of results from case series or RCTs with different inclusion criteria, but where there is no direct RCT evidence of benefit and risk .

INTRODUCTION

The colloquial definition of sciatica is pain in the buttock and leg and it is a term understood by the nonprofessional population. The anatomic pathology is usually caused by lumbosacral disc herniation and degenerative lumbosacral spondylosis involving the L2/3 to L5/S1 intervertebral discs and foramina.[1] Therefore sciatica can be associated with numbness, paraesthesia and weakness in the leg. The terms radicular pain and radiculopathy describe this neurological component of the pathology by health-care professionals and researchers.[2] Radicular pain is thought to arise from ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots from ischaemia or inflammation.[3] Radiculopathy indicates that there is conduction block of the spinal nerve or its roots from either mechanical compression or ischaemia. Nonetheless, the terms are still used interchangeably and inconsistently in the randomised controlled trial (RCT) literature.[4],[5] This study defines the term sciatica as radicular pain with or without radiculopathy from lumbosacral nerve root pathology. The definition of acute sciatica in the RCT and systematic review literature also differs. It has been defined as less than 4 weeks, less than 6 weeks and less than 12 weeks duration. Subacute sciatica is usually between 6-12 weeks duration. Chronic sciatica is greater than 12 weeks duration. In this protocol symptoms less than 4 weeks duration are defined as acute.

The prevalence of lumbosacral radiculopathy has been estimated at 3% to 5%[6], whereas referred leg pain is much higher.[4] In an inception cohort of 1,172 patients with acute low back pain presenting to primary care settings in Australia, 25% had leg pain[7]. The majority of participants (72%) with acute sciatica recover completely by 12 months[7]. In another study, 50% of patients with acute sciatica recovered within 4 weeks. However, 30% had persistent leg pain and disability at 12 months[8].

Patients with acute sciatica are treated with a combination of paracetamol, opiate analgesia, non-steroidal anti-inflammatory drugs (NSAIDs)[9-11] pregabalin, and physiotherapy although a systematic review of pharmacologic therapy that included NSAIDs, opioid analgesics, antidepressants, anticonvulsants, muscle relaxants, and opioid analgesics, showed no effect or only small effects in acute, subacute and chronic sciatica[12]. Neuropathic symptom modifiers such as pregabalin have also recently been shown to be ineffective[13].

During the 1970s, failure of conservative management in sciatica and the desire to avoid surgery led to interventional procedures, including epidural steroid injections (ESI). There are three approaches for epidural steroid injections: caudal, interlaminar and transforaminal. The transforaminal approach deposits steroid directly near the ventral epidural space at the affected unilateral nerve root level. Evidence for the superiority of the selective transforaminal approach versus the caudal and interlaminar is generally indirect[14] as there are few high quality head-to-head studies[15]. Selective fluoroscopy (with or without computed tomography (CT) guided fluoroscopy) transforaminal epidural steroid injection (TESI) with local anaesthetic, colloquially described as a "spinal perineural steroid injection", is increasingly being used in the management of patients with acute sciatica in hospital and community settings in the absence of any RCTs undertaken to evaluate the benefit of this procedure in patients with acute sciatica. There are no Cochrane reviews on the management of acute sciatica with epidural steroids of any route[16]. In reviews of epidural steroid injections (caudal, laminar or transforaminal) in sciatica of any duration, not surprisingly, given the heterogeneity of patient populations, interventions, study design and study conduct, conclusions vary considerably. Two recent meta-analyses of epidural steroids in subacute and chronic sciatica [17],[14] conclude that treatment effects are small and of only short duration.

The first transforaminal approach RCT was published in 2000[18]. Five RCTs have been published[19-23] that have had low risk of bias from random sequence generation and participant and personnel blinding. These RCTs show considerable heterogeneity in study design. All RCTs

except one required a symptom duration of at least 4 weeks prior to recruitment. No RCT used CT fluoroscopy. All but one RCT required magnetic resonance imaging (MRI) evidence of disc herniation[18] . Two studies excluded patients with evidence of foraminal stenosis [21 23]. Three studies did not report neurological features.[20],[22],[23] All studies included an epidural control, but only one study also included a non-epidural control[21]. Only two studies clearly specified the primary endpoint[21],[22], but these two studies had incomplete follow-up as they did not obtain further data on patients who failed to achieve a 50% reduction of pain 4 weeks after the last procedure. Where epidural saline was used as an epidural control, speculated mechanisms for a therapeutic effect include washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.[21],

Harms have been reported with transforaminal epidural steroid injections[24] including infection and bleeding. In 2014, the Food and Drug Administration (FDA) issued a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including "loss of vision, stroke, paralysis, and death." [25]. The risk is greater for particulate versus non-particulate steroids and in cervical versus lumbosacral epidurals. Recently a consensus opinion paper was published on safeguards to prevent neurologic complications after epidural steroid injections[26]. The clinical considerations were based on conventional fluoroscopy with contrast and not with CT fluoroscopy. RCTs show no difference in efficacy between particulate and non-particulate steroids[27-29].

Unlike epidural steroids, systemic steroids have been studied in acute as well as subacute sciatica. A meta-analysis of 7 small of studies of variable quality of intramuscular (IM), intravenous (IV) and oral steroids found steroids were not superior to placebo and had more adverse events[30]. Adverse events, however, were clearly related to the very high dose of dexamethasone used in 3 of the 7 studies (120 mg of dexamethasone in 3 days which is the equivalent of 800mg of oral prednisone). In another systematic review[12] three studies of acute sciatica using smaller doses of steroid, a significant effect on short-term overall pain and leg pain was found. A RCT of IM steroid versus IM saline failed to show a difference in leg pain scores[21]. A blinded RCT reported that IV dexamethasone (8mg) improved pain scores at 24 hours and reduced ED length of stay compared to placebo. There was no difference at 6 weeks[31]. No CT/MRI imaging evidence was required. A recent blinded RCT of patients of oral steroids (prednisone 60mg 5 days, 40mg 5 days and 20mg 5 days) with sciatica less than 12 weeks duration showed an improvement in function at 3 weeks and 52 weeks but no improvement in pain[32].

In summary, there are two issues that are relevant that provides the rationale for this pilot/feasibility study (i) the condition under study i.e. acute, subacute or chronic sciatica, (ii) the route of interventional procedure (caudal, interlaminar and fluoroscopic transforaminal epidural (the last with or without CT guidance) or systemic route. There are no RCTs in acute sciatica published using steroid epidurals of any type. There are RCTs in acute sciatica with systemic steroids. In subacute and chronic sciatica there are no RCTs that have used selective CT fluoroscopy transformational steroid injection, indicative of the fast pace of changing technological procedural interventions without RCT evidence. Arguably, steroids may be more effective for sciatica when provided in the acute setting, but this should be subjected to rigorous evaluation. In Australia selective transforaminal epidural steroids is guided by computed tomography (CT) fluoroscopy, therefore is performed by interventional radiologists. Given their use and perceived effectiveness, and the costs and potential harms associated with their use, there is an identified need to properly evaluate the use of epidural and systemic steroids in acute sciatica in adequately controlled trial designs with a control arm for the route of procedure. Furthermore, given that there is a rationale for the benefit of epidural saline in acute sciatica, epidural steroid could be directly compared to epidural saline to evaluate pharmacology versus a simple physical washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.

There is a clear advantage of directly comparing different interventions in a single randomised control trial. These advantages include improving internal validity, marginally reducing sample size, and limiting heterogeneity by standardising assessments and conduct procedures. However, there are also disadvantages such as longer time to trial recruitment, therefore longer time to trial completion, more exclusion criteria because of differing interventions, and difficulty explaining design to participants.

METHODS / ANALYSIS

Study Objectives

Primary objective

Undertake a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of a blinded 4-arm RCT of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days of a tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of corticosteroid intervention by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline and includes blinding with oral placebo and sham injection across all arms. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. The primary analysis is comparison of CT fluoroscopy guided transforaminal lumbar epidural steroid versus sham injection (Arm 1 versus Arm 4 in Figure 1. Study Design).

The pilot/feasibility study will evaluate the following issues: rate of recruitment, study conduct including randomisation allocation concealment, preparation of interventions, choice of procedural corticosteroid and local anaesthetic, blinding, efficient organisation of initial assessments, diagnostic imaging, and ensuring efficient study processes across public/private hospital inpatients, emergency department /room (ED/R) presentations and general practice visits, and timeliness of providing the intervention within the 4 week acute sciatica requirement. Rate of recruitment is important particularly where there already is an expectation of treatment benefit “spinal perineural steroid injections” by health care professionals and patients.

This pilot/ feasibility study is a single centre Human Research Ethics Committee (HREC) study, but includes recruitment from multiple sources and the interventions will be delivered in public hospital, private hospital and community radiology practices. The recruitment of participants and the delivery of the interventions have been designed to identify feasibility issues given these different settings.

Secondary objectives

1. Obtain preliminary results from this RCT which will be used to calculate the sample size and power calculations for a full-scale study of treatments currently used in the management of acute lumbosacral radiculopathy of less than 4 weeks duration is the most effective in reducing pain and disability in the short-term and prevent progression to persistent or recurrent lumbosacral radiculopathy in the long term.
2. Evaluate the adequacy of outcome measures in acute sciatica, where pain, sensory and motor neurological symptoms all cause distress and disability, and where pain caused by nerve root irritation often progresses to loss of pain and may be replaced by sensory loss or weakness from nerve root conduction impairment. The importance of describing this multifactorial pathology and how it impacts the primary endpoint, the Oswestry Disability Index has substantive importance regarding the optimal primary and secondary endpoint for use in a full-scale RCT. Other outcome measures will also be evaluated such as confounding by medication use and taper, protocol compliance and burden, confounding by modification of activities and need and timing of rescue procedures.

3. Although this is a feasibility study, for transparency the following are the pre-specified hypotheses for powering a full-scale RCT. In patients with acute sciatica, selective CT fluoroscopy transforaminal lumbar epidural steroid (Arm 1) is (a) superior to control (Arm 4) and (b) non-inferior to a 15 day tapering dose of oral dexamethasone (Arm 3) in reducing short-term pain and disability (after 3 weeks) as determined by the Oswestry Disability Index. Further information regarding hypotheses and sample size is described in the sample size section.

Participants, interventions and outcomes

The study setting is the rheumatology service at a large teaching hospital in Sydney, Australia. The teaching hospital services a population of about 1 million of Southern Sydney. The eligibility criteria are as follows:

Inclusion criteria

(i) leg pain of any description with clinical findings consistent with single level radiculopathy,
(ii) minimum symptom duration > 72hrs,
(iii) maximum symptom duration < 3 weeks to ensure symptom duration at randomisation is < 4 weeks,
(iv) no previous episode of same level radicular pain in the previous 6 months,
(v) pain intensity at >30 on the Oswestry Disability Index (ODI),
(vi) imaging (MRI and/or CT) indicating herniated disc or foraminal stenosis or both, concordant with the level indicated by history and physical examination,
(vii) age at least 18 years

Exclusion criteria

(i) previous transforaminal epidural steroids at any level in the last 12 months,
(ii) previous oral steroids in the last 12 months,
(iii) any lumbar surgery at same level, or above or below the level at any time,
(iv) previous lumbar surgery at any other level to that in (iii) within the last 12 months,
(v) pregnancy, or lactation/breastfeeding
(vi) direct indication for neurosurgery (e.g. cauda equina syndrome, or progressive motor loss i.e. ≤ 3/5 power),
(vii) inability to read or understand English
(viii) any serious medical or psychiatric condition that may interfere with participation or outcome assessment such as: need for uninterrupted anti-coagulation, spinal fracture, active infection or metastatic disease suspected, active cancer, poorly controlled diabetes, or patients with diabetes on any insulin, uncontrolled hypertension (systolic blood pressure >180 or diastolic blood pressure >110 within 30 days of randomization date), active peptic ulcer disease, history of intolerance to steroid therapy, previous or current psychiatric history of bipolar disease, or secondary gain such as anticipated or ongoing legal proceedings, history of substance abuse
(ix) no other pathology likely to explain condition (e.g Guillain-Barre Syndrome, vasculitis)

Both MRI and CT scan are acceptable for entry criteria. If CT is equivocal regarding pathology or level, then the patient will proceed to MRI, or the patient is not included in the study. Scans are performed without contrast. All potential participants will be reviewed by a study physician (rheumatologist) who will undertake a history and physical general, musculoskeletal and neurological examination to ensure inclusion and exclusion criteria and exclude 'red flags' and alternate diagnoses. Full laboratory examination of safety includes full blood count (FBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), coagulation profile, electrolytes, urea, creatinine (EUC), liver function tests (LFTs), fasting blood glucose. Patients who can cease

antiplatelet and anticoagulant medications safely will be given instructions on how to do so, or are excluded. The CT and/or MRI images are reported by an experienced radiologist who is unaware of the study, and the results are discussed with the participant and their treating physician. If the report is unclear, the images are reviewed by an independent radiologist at a radiology meeting to clarify imaging pathology. If imaging pathology remains unclear then eligibility is not met. The images are also reviewed by the interventional radiologist prior to the procedure (see Implementation). If the interventional radiologist cannot confirm the specified imaging pathology the procedure is aborted and the principal investigator is contacted.

Interventions

The interventions are as follows and also summarised in Table 1 and Figure 1.

Procedural interventions. Once the specific spinal nerve pathology has been selected clinically and on imaging (e.g. right S1 nerve root at L5/S1 intervertebral space), all participants are given an injection of local anaesthetic (lignocaine or bupivacaine) into the skin and subcutaneous tissue at this selected site.

Participants in Arm 1 will receive selective CT fluoroscopy transforaminal epidural dexamethasone 4mg (1ml) a non-particulate corticosteroid with the local anaesthetic lignocaine 1% (1ml). However, if participants are an inpatient at St George Hospital they will receive betamethasone (1ml) as celestone chondrose 5.7mg/ml, a particulate corticosteroid with the local anaesthetic bupivacaine 0.5% (1ml). This is at the direction of two interventional radiology investigators who have differing preferences regarding procedural agents. The interventional radiologist and their preference is known and will be addressed in the hierarchical linear model analysis.

Participants in Arm 2 will receive selective CT fluoroscopy transforaminal epidural 0.9% normal saline (1ml) and lignocaine 1% (1 ml) unless they are hospital inpatients in which case they will receive bupivacaine 0.5% as the local anaesthetic agent. The saline epidural has two purposes in this pilot/feasibility study. There is no consensus in the literature regarding the optimal control for the evaluation of epidural steroids [33]. Moreover, there is some evidence that it has a therapeutic effect[21]. Therefore this pilot/feasibility study is designed to explore these issues by including both epidural saline arm (Arm 2) and a sham injection (Arms 3 and 4).

Participants in Arms 3 and Arms 4 will receive sham selective CT fluoroscopy intramuscular injection with needle placement down to muscle layer and no injection of any fluid. The intervention is performed by an experienced interventional radiologist. The intervention radiologist is not blind to the procedure (see section Blinding, for more information).

Oral intervention. The oral steroid is dexamethasone. The 15 day taper dosing is (i) 4 mg at 8am and 6pm days 1-5, (ii) 2 mg 8am and 6pm days 6-10, and (iii) 1mg 8am and 6pm days 11-15. Dexamethasone has a longer biological half-life than prednisolone. The oral interventions are over-encapsulated in gelatine capsules packed with sucrose and lactose. The placebo is sucrose and lactose only. Participants in Arm 3 receive the oral dexamethasone capsules, and participants in Arms 1, 2 and 4 receive the placebo capsules. Dexamethasone and placebo capsules have identical appearance and are prepared by a compounding pharmacist. The capsules are placed in three plastic bottles with clearly labelled instructions. At each telephone or in-person contact treatment adherence is monitored.

Concomitant management and interventions: All participants have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. All concomitant therapy will be recorded at each visit. Rescue therapy includes CT fluoroscopy transforaminal epidural of steroid and neurosurgery.

Table 1: Summary of the experimental interventions by Arm

Arm	Experimental intervention
Arm 1 **Intervention 1** Injectable Dexamethasone and Lignocaine OR Betamethasone and Bupivacaine selective CT fluoroscopy guided transforaminal lumbar epidural steroid	**Drug: Betamethasone OR Dexamethasone Injectable** Procedural agents. The steroid and local anaesthetic preparation is determined by interventional radiologist's preferences regarding the use of particulate or non-particulate steroids. Dexamethasone 4mg (1ml) is a non-particulate corticosteroid and is used with the local anaesthetic lignocaine 1% (1ml). Betamethasone Sodium Phosphate/Acetate 5.7 mg/ml Injectable is a particulate corticosteroid and is used with the local anaesthetic bupivacaine 0.5% (1ml). Other Name: celestone chondrase 5.7 mg/ml injectable suspension Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 2 **Intervention 2** Normal Saline Flush, 0.9% Injectable Solution with either Bupivacaine or Lignocaine selective CT fluoroscopy guided transforaminal lumbar epidural normal saline	**Drug: Normal Saline Flush, 0.9% Injectable Solution** Procedural agents. The local anaesthetic preparation used with the Normal Saline Flush, 0.9% Injectable Solution, will be standardized to replicate current radiology interventional practices: either local anaesthetic bupivacaine 0.5% (1ml) or local anaesthetic lignocaine 1% (1ml). Other: Sham injection and/or oral placebo The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 3 **Intervention 3** Dexamethasone oral capsule 15 day tapered dosing as follows: (i) days 1-5, 4 mg morning and evening, (ii) days 6-10, 2 mg morning and evening, and (iii) days 11-15, 1mg morning and evening.	**Drug: Dexamethasone Oral Tablet** Dexamethasone Oral Tablet: 15 day taper dosing is: days 1-5 8mg (4mg morning and evening) , days 6-10 4 mg (2mg morning and evening), and days 11-15 2 mg (1mg morning and evening). The dexamethasone is over-encapsulated in a gelatine capsule that is identical to the placebo capsule in appearance. Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 4 **Control** Sham injection and/or oral placebo: CT/ fluoroscopy guided (parameters set to zero) transforaminal lumbar sham (needle placement down to muscle and no injection of any fluid) AND placebo oral tablets taper.	**Sham Injection and/or oral placebo** The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.

Outcomes

A recent publication on core outcomes domains for clinical trials in non-specific low back pain recommended physical functioning, pain intensity, and health-related quality of life [34].

Primary outcome measure.

The Oswestry Disability Index (ODI) version 2.0 [35] is the primary outcome measure. The ODI is a functional status measure specifically developed for disorders of the spine and has been used in most RCTs of sciatica[36] and see Table 2. It is a 10-domain 2-page 5 minute questionnaire with ordered 6-response-item (0-5) scales for each question. The questions address domains of pain, physical functioning, sleeping, home/work functioning and impact on social life. The scores are summed, then doubled and the final score is 0-100. The ODI will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48. This will be administered at visits, phone or mail. The primary analysis is the short-term outcome, reduction of disability at 3 weeks on the ODI. The secondary analysis is the long-term outcome, reduction of disability at 48 weeks on the ODI.

Secondary outcomes.

Numerical Rating Scale (NRS) for leg pain is the main secondary outcome. A measure of leg pain is included in all studies of sciatica. The NRS is a validated[37] 11 point scale. Participants will be asked to rate their average leg pain over the preceding 24 hours. Zero represents 'no leg pain' and 10 represents 'worst imaginable pain'. Although the Visual Analogue Scale (VAS) is a more frequently included measure, unlike the VAS, the NRS can be verbally administered by phone. This will be administered at Eligibility Baseline/Randomisation (day 0), day 1-7, weeks 2, 3, 6, 12, 24, 48.

Numerical Rating Scale (NRS) for back pain. The severity of back pain may differ to that of leg pain so both measures are needed. It is rated as an average over the preceding 24 hours and will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Pain DETECT Questionnaire [38]. At Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Short-Form 36 (SF-36) questionnaire [39] evaluates health related quality of life and will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48.

Lumbosacral and lower limb musculoskeletal and neurological history and clinical examination at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. This includes inspection of gait, lumbosacral spine and lower limbs for scoliosis, asymmetry, loss of lumbar lordosis, abnormal gait and stance, weakness, muscle wasting, muscle fasciculation, palpation of lumbosacral spine for tenderness and rigidity, movement of lumbosacral spine in flexion and extension, hip, knee and ankle range of movement, straight leg raise and femoral stretch test. Neurological examination of lower limb includes further inspection, examination for tone (normal, increased, decreased), clonus (present absent and beats of clonus if present), power (0, 1, 2, 3, 4, 4+ and 5 out of 5) for 12 lower limb movements (hip abduction, adduction, flexion, extension, knee flexion and extension, ankle dorsiflexion, plantar flexion, inversion and eversion, big toe extension and flexion) , knee and ankle reflexes (increased, normal, decreased absent), plantar reflexes (normal, up-going, equivocal, no response), and pinprick, light touch, proprioception and vibration sensory examination.

Work and health utilisation measures at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. These will include days missed from paid employment (if applicable) because of sciatica, use of health services such as doctor, other health-care provider related visits (e.g. acupuncture, chiropractic), injection procedures and neurosurgery. This information will be obtained by interview at each visit and is documented in the case report form developed for the study.

Demographic and socioeconomic measures measured at baseline include age, gender, and occupation/previous occupation.

Imaging findings on CT and /or MRI will be used to define the site, level, type and degree of pathology using classification systems for disc herniation [40] and severity of nerve root compression [41]. This data will be used to determine imaging predictors of response.
Medications: use of all other medications including analgesics, NSAIDs, opiates, gabapentin and pregabalin will be documented at every visit.

Economic evaluation: Outcomes for an economic evaluation will also be collected in this feasibility study. The feasibility of a cost-effectiveness analysis will be undertaken using the ODI and a cost-utility analysis [42] using the EQ5D-5L for incremental costs per quality-adjusted-life-year (QALY)[43]. The EQ5D-5L questionnaire will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. Work and health utilisation measures described above will also be collected. Costs within each randomised arm will be assessed in terms of hospital, health care visits, investigations, such as CT and MRI imaging, procedure costs and medications costs. These direct costs are determined with Diagnosis Related Groups cost weights for hospital in-patients, and for outpatients by the Australian Medical Benefits Scheme standard fees, and the Australian Pharmaceutical Benefits Scheme (PBS). These costs are determined by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) Manual of Resources items and their associated costs used for economic analyses[44], [45]. The PBAC does not require questionnaires of productivity[44],[45] such as the PRODISQ[46] and similar questionnaires of resource utilization.[47]
Adverse events will be collected at day 1, day 7, weeks 3, 6, 12, 24, 48. These will include steroid adverse effects (blood pressure, blood glucose, changes in mood and sleep) and procedural adverse effects (headaches, bleeding) and information about additional procedures, surgery and hospitalisations.

Table 2: Schedule of enrolment, interventions and assessments

	STUDY PERIOD											
	Screening& Eligibility	**Allocation**	**Post allocation**									**Close-out**
TIMEPOINT	-T1	0	T1	T2	T3		T4	T5	T6	T7	T8	T9
D=Day W=Week		**D0**	**D1**	**D 2-6**	**D7**	**D 8-15**	**D14**	**D21**	**W6**	**W12**	**W24**	**W48**
ENROLMENT												
Eligibility Screen	✓	✓										
Neurological and musculoskeletal Examination	✓	✓										
Safety Blood Tests	✓	✓	✓		✓			✓				
MRI (or CT if MRI contraindicated or CT clearly demonstrates imaging pathology)	✓											
Oswestry Disability Index	✓	✓										
Informed Consent	✓											
Allocation		✓										
INTERVENTIONS												
Procedural injection in radiology suite		X										
Oral medications		X	X	XXXX	X	XXXX XXXX						
ASSESSMENTS												
Outcome Variables												
Oswestry Disability Index	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Numerical Pain Rating Scales	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
PAIN DETECT Questionnaire	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
SF-36	✓	✓			✓		✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Work/health utilisation/costs	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Medication History	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Neurological and musculoskeletal Examination			✓		✓			✓	✓	✓	✓	✓
Safety Blood Tests			✓		✓							
Other Data variables												
Rescue procedure history			✓		✓			✓	✓	✓	✓	✓
Participation Randomization perception			✓		✓			✓	✓	✓	✓	✓
Adverse Events & Serious Adverse Event Assessment		✓	✓	✓	✓			✓	✓	✓	✓	✓

Sample size

Most trials of subacute and chronic sciatica of a selective CT fluoroscopy transforaminal epidural steroid injection have a sample size of 30 participants per arm. The primary outcome in this pilot/feasibility study is the ODI at 3 weeks comparing epidural steroid and sham injection (Arm 1 vs. Arm 4). With 15 participants per arm, there is 85% power to detect a difference of 17 ODI points between these two arms, given a standard deviation of change of ODI of 15.1 points[32]. Statistical test on which calculation is based is the independent two-sample t-test with a two-tailed alpha of 0.05 (Stata 14). This is a total of 60 participants in this pilot/feasibility study. This is sufficient to evaluate feasibility of the study design, study conduct and determine sample size for a full-scale multicentre study. However, this ODI difference is a large unrealistic effect. The minimum clinically important difference in ODI scores in one study was 7.0 points [48], and an international consensus group found empirical evidence of 4 to 15 ODI points[49] and recommended a cutoff value of 10 ODI points. Given that we are recruiting participants with acute sciatica of less than 4 weeks duration, an ODI difference of at least 10 ODI points is very reasonable. A sample size of 49 participants per arm will provide 90% power to detect a minimum clinically important difference of 10 ODI points assuming a standard deviation of 15.1 with a two-tailed alpha of 0.05 (Stata 14). Allowing for 20% dropout (which at 3 weeks is unlikely but at 48 weeks is more likely), 236 participants will be recruited, 59 to each arm. Although there are 6 possible comparisons in a 4 arm trial, controlling for type-1 error rate is not needed when several different experimental arms are compared with the control[50],[51]. Therefore no multiplicity adjustment is needed for: (i) Comparison I- Arm 1 versus Arm 4 (epidural steroid is superior to control), (ii) Comparison II - Arm 2 versus Arm 4 (epidural saline is superior to control), and Comparison III - Arm 3 versus Arm 4 (oral steroid is superior to control). However, in order to proceed to Comparison IV, Arm 1 versus Arm 3 (epidural steroid is superior to oral steroids), we must first demonstrate that Comparisons I and III were statistical significant, and there must be a type-1 error consideration[52]. Furthermore, if the hypothesis is that oral steroid is non-inferior to epidural steroids, then the ignorable difference must also be prespecified. The pilot/feasibility study will provide data that will be helpful in determining these sample size calculations. The feasibility study will be informative regarding the estimated mean difference in this population, its standard deviation, and pattern of missing data at each of the study visits.

Recruitment processes

Participants will be recruited from (i) Emergency departments (EDs) of public hospitals, (ii) current inpatients of public and private hospitals and (iii) referral from community general practitioner or medical specialist (rheumatologist, neurosurgeon or orthopaedic surgeon) from the Sydney metropolitan area around St George Hospital. It is anticipated that the majority of participants will be recruited from emergency department presentations and general practitioners. Participants with sciatica symptoms less than 21 days duration are screened so that participants can be evaluated and undergo the allocated intervention within the 4 weeks eligibility criteria.

St George Hospital Emergency Department, as well GPs and relevant specialists in the geographic area (population approximately 270,000) serviced by this hospital area have been provided information about SCIATICA study, the inclusion/exclusion criteria, explanation of the trial rationale, and the opening of a daily acute sciatica clinic at St George Hospital centre as the portal of entry for trial patients.

Participants presenting to the Emergency Department (ED) with acute sciatica are assessed according to ED's usual procedures and staff admit or discharge patients according to their usual care pathway. If the ED does not admit a potential acute sciatica participant, a study clinician is contacted by phone Monday-Friday 9am to 5pm (business hours) and a referral is faxed. Out of business hours, a referral is faxed to the acute sciatica clinic which is processed the next business

day (see below). All referred participants are given a brochure by the referring ED clinician outlining the study. The acute sciatica clinic is also available for urgent referrals from community general practitioners and specialists. This is by fax or by telephone. These referred participants are also given a brochure by their referring clinician. All referred potential participants are logged. Within 1 to 3 days, Monday to Friday, all referred participants are contacted by telephone by a study clinician and a telephone history is obtained to ascertain suitability regarding inclusion and exclusion criteria. Where eligibility is clear or indeterminate, an eligibility visit is organised within the next couple of days. At this visit a full history and examination, musculoskeletal and neurological is conducted to determine underlying pathology, and if acute sciatica is likely, then lumbosacral imaging preferably with MRI imaging and blood pathology is requested. Patients complete routine clinical practice questionnaires as part of clinic audit including ODI, SF-36 and EQ-5D-5L. Conservative therapy is initiated (medication/physiotherapy) as appropriate. Potential participants are provided with the Participant Information and Consent Form and further information regarding the RCT if eligibility criteria are likely. Once imaging and pathology becomes available the participant is contacted and informed of the results. If s/he meets the criteria s/he is invited to participate in the RCT. At one of the visits prior to randomisation, all participants are reviewed by the principal investigator to ensure that all eligibility criteria are met. This includes a full general, musculoskeletal and neurological history and clinical examination and confirmation of imaging. If eligibility criteria are met and the participant agrees to participate, then the participant proceeds down study pathway. Processes are in place to ensure that enrolees, if they agree to participate, are safely fast-tracked to randomisation and RCT interventions.

If patients do not agree to participate in the RCT they can either decide to continue their management in the acute sciatica clinic, and if their general practitioner is willing then the patient's ongoing management is determined by the rheumatologists who run the acute sciatica clinic. If the patient wishes to be managed by their GP, a letter from the acute sciatica clinic is sent to the GP to facilitate management. The patient has the option of returning to the acute sciatica clinic for further management or advice as needed. A log of potential participants who decline or are ineligible for any reason is kept for later evaluation consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines[53]. Reason for rejection or refusal will be recorded if available as well as age, gender, race/ethnicity and ODI score. If the participant does not wish to participate in the RCT but wish to be managed in the acute sciatica clinic they are included in a clinical audit of the management of acute sciatica. The management is determined in consultation with the patient and is generally conservative therapy unless there is severe pain and progressive functional disability preventing return to work or normal activities, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

The participant may clearly not meet the eligibility criteria at telephone screening. If patient safety is not an urgent consideration, patients who have anticipated or ongoing legal proceedings, need uninterrupted anti-coagulation or active cancer (as exclusion criteria) are not progressed to the eligibility visit but are asked to see or return to their treating doctor. Participants that do not have any leg pain are also asked to see or return to their treating doctor. However, if a referred patient has a history that suggests cauda equina syndrome or symptoms suggestive of malignant or infection-related pathology, the patient is seen urgently in the acute sciatica clinic and appropriate investigations and management are instituted.

If the participant does not wish to participate they are included in a clinical audit of the management of acute sciatica during the admission and the participant is continued to be managed according to the treating clinician. This is generally conservative therapy unless there is progressive severe pain and functional disability preventing discharge, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

If the participant is admitted to hospital with acute sciatica the admitting team will contact the study investigators. Most patients with acute sciatica in our setting are either admitted under the general medical team, the rheumatology team or the neurosurgical team. The same processes are followed for in-patients as described above for out-patient referrals. Only a study investigator can consent a participant to participate in SCIATICA

All participants are told that participation is voluntary, they can discuss participation with family, friends or their health care practitioners, and if they decide not to participate, it will not affect the treatment they receive now or in the future. They can have family and friends with them during the consent process. They can also withdraw from the study once it has started, at any time without having to give a reason.

Assignment of interventions

Sequentially numbered, opaque and sealed envelopes contain the randomised intervention. Participants are randomly allocated 1:1:1:1 by computer-generated random numbers using permuted blocks stratified by duration of sciatica (≤2 weeks, >2 weeks). The randomisation schedule including details of blocking schedule are held off-site by the randomised allocation sequence study investigator who is not involved in participant recruitment , assignment of interventions or data collection to ensure allocation concealment. This study investigator places the study medications and procedure instructions for each arm in separate opaque sealed envelopes. These two envelopes in turn are placed into a single larger opaque sealed envelope labelled with a sequential number and the randomisation number. The sealed envelopes are held in a locked cabinet until retrieved by the blinded study investigators who are involved in participant recruitment, provision of the study interventions, participant management and data collection. The acute sciatica clinic study investigators are blind to the study intervention.

Implementation of interventions

The day of study intervention implementation, the participant has safety bloods performed, unless eligibility safety bloods had occurred in the previous week. The participant completes the study questionnaires and the study clinician once more ascertains eligibility criteria by history and examination immediately in the morning before attending the radiology suite. If the criteria are still met the study clinician indicates the exact site of the CT fluoroscopy transforaminal epidural on a request form that is provided to the interventional radiologist. For example, “perform a selective CT fluoroscopy transforaminal epidural of corticosteroid and local anaesthetic at L5/S1 targeting the right S1 nerve root”. The MRI images are also provided to the interventional radiologist. The research officer retrieves the next in sequence numbered large opaque labelled sealed envelope. The research officer accompanies the participant, taking the interventional request, images (films or on CD) and large opaque labelled sealed envelope to the radiology suite. At the radiology suite the research officer opens sealed opaque envelope, gives the ‘procedure’ envelope with instructions to the radiologist and exits. The radiologist evaluates the MRI images, then opens the procedure envelope. It contains one of three instructions: (i) selective CT fluoroscopy transforaminal epidural steroid and local anaesthetic injection, (ii) selective CT fluoroscopy transforaminal epidural normal saline and local anaesthetic injection or (iii) intramuscular sham injection down to muscle layer but no injection of any fluid. The side (right or left) and lumbosacral level (e.g L5/S1) is determined by the radiology request form. The participant is positioned prone as per a CT fluoroscopy transforaminal epidural, the CT fluoroscope is positioned as if a CT fluoroscopy transforaminal epidural is performed, local anaesthetic is injected into the skin and subcutaneous tissue. Radiologist and his staff maintain patient blinding. CT/fluoroscopy guided transforaminal lumbar epidural radiation parameters are set to reduce radiation dose. There is no radiation dose for CT/fluoroscopy guided transforaminal lumbar sham injection because the parameters are set to zero although the machine is on. All CT fluoroscopy images are saved for further analysis.

At the end of the procedure once outside the CT fluoroscopy room, the research officer gives the opaque envelope marked "Dexamethasone or placebo capsules" to the participant and explains how the medications are to be taken over the next 15 days. There are three plastic bottles labelled Days 1-5, Days 6-10 and Days 11-15. The participant opens the Day 1 labelled bottle and swallows the capsule. The participant continues to lie flat for at least one hour after the procedure, the participant is forbidden to drive for 24 hours and a person accompanies them home. The interventional radiology procedure report states that the participant had a procedure as part of the SCIATICA RCT and to contact the chief investigator if there is a concern, a phone number is provided.

Masking/Blinding.
All personnel except the radiologist delivering the procedure and the investigator responsible for randomisation and preparing the interventions will be blind to the randomisation arm. The trial participant, study clinicians, research officers, participant's treating care providers, outcome assessors, and data analysts are blind to the intervention assignments. In the event of a serious medical emergency during which the treating doctor must know in which arm the participant was randomised, the randomised code can be broken. Each participant is given a 24 hour emergency contact number and the principal investigator contacts the investigator who holds the randomisation schedule to determine the participants allocated intervention.

Data collection, management and analysis
Data collection methods
Data quality of outcome, baseline and other trial data is safeguarded with standardisation, assessor training and duplication of measurements and assessments by research officers administering the questionnaires and study clinicians undertaking the history and clinical examinations. All assessments are reviewed and the history and clinical findings confirmed by the principal investigator prior final eligibility determination. Study clinicians meet every 2 weeks to discuss ongoing assessments, issues of standardisation, equivocal or unclear findings and or any other concerns. All questionnaire data is scanned, with range checks for data values, and verified. Free text data scanned and verified. Clinical data is coded and verified. Participants' retention and complete follow-up is encouraged through contact by phone or text and visits are organised so that they are maximally convenient for participants. This often requires visits to be conducted at the end of the normal working day.

Data/Statistical Analysis Plan
Although this is a pilot/feasibility study to evaluate several important clinical and trial design considerations the following data analysis plan is proposed for transparency. In this feasibility study treatment is analysed by intention-to-treat and the data analyst will be blind to arm allocation. A two-tailed p-value <0.05 is considered statistical significant. The primary analysis is an analysis of variance evaluating the effects of treatment on the ODI at week 3, using treatment arm, baseline ODI and duration of symptoms in days as covariates. The primary comparison is epidural steroid versus control. However, similar analyses will be applied to the other treatment comparisons with control (epidural saline versus control, oral steroid versus control) without a type-1 error penalty. However, the epidural steroid versus oral steroid comparison will require type-1 error consideration[52]. All comparisons are made at Day 21, where Day 0 is the day of the procedural intervention immediately followed by the first dose of the oral intervention. Day 21 is the 3 week endpoint.

Similar analyses will also be applied at the 6 and 48 week endpoints for the ODI. Multilevel linear mixed model will examine time trend by treatment arm interaction. This linear mixed model will be used to model ODI trajectory across all 10 time-points by treatment arm, where treatment arm is a property of the persons and visit is nested within person. The random-effects portion of the model is time which here is the measurement at each month as the random effect. Analyses will be

undertaken unadjusted and adjusted for (i) medication use, (ii) presence of a definite motor radiculopathy (iii) days from onset of sciatica pain to delivery of the intervention, (iv) whether the imaging demonstrates a prolapsed disc, a sequestered disc or a extruded disc fragment, (v) whether imaging demonstrates bony/osteophytic narrowing of the neural exit foramen , and (vi) age. Missing data will be handled with multiple imputation, using iterative Markov chain Monte Carlo (MCMC) which requires the assumption that the data are missing at random[54]. An intention to treat analysis with multiple imputation is the primary analysis, however, a completers analysis will also be undertaken as a secondary analysis. The value of undertaking a feasibility study is that patterns and reasons of missing data that are not at random may be identified and in the full-scale study targeted efforts made to reduce this potential bias. There is no interim analysis.

Other outcome measures (NRSs, SF-36, EQ-5D and clinical data measured on a continuous scale) will also be analysed with multilevel mixed effects linear regression. All analyses will be undertaken unadjusted and adjusted for other medication use, type of procedural steroid, presence of neurological signs, and MRI findings with multivariate methods. A full description of neurological signs will be reported in tabular form and descriptive statistics. Safety data will be analysed in reported in tabular form and with descriptive statistics.

Economic Evaluation

This feasibility study will provide data to identify issues conducting an economic evaluation for the full-scale study. The rationale for undertaking an economic evaluation is to evaluate the feasibility of undertaking a pre-specified cost-effectiveness economic evaluation in the full-scale study. In Australia, all drugs and more recently, certain procedures, undergo a cost-effectiveness analysis to determine whether they will be subsidised by the Australian government. This is usually performed from the perspective of the health-care sector rather than from the societal perspective[44]. We will be following these guidelines. In this pilot/feasibility study we will ascertain the feasibility of obtaining the outcome (including QALYs) and cost data in a valid manner, determine how much outcome and cost data are missing, and obtain estimates of mean and standard deviation of outcomes and costs. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[42] statement checklist will also be followed to report the economic evaluation component in the full study.

In this pilot/feasibility study all participants in all study arms have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. *Arm 4, the control arm, therefore is the usual care arm.* In this pilot/feasibility study the perspective of the health sector is undertaken using intention-to-treat. The incremental cost per point on the ODI or QALY (based on EQ5D-L) will be estimated as the ratio of the difference in average cost and ODI or QALY between intervention arms for three comparisons: (i) epidural steroid vs. control, (ii) oral steroid vs. control, and (iii) epidural steroid vs. oral steroid. Missing data will be imputed with iterative Markov chain Monte Carlo methods. Sensitivity analyses will be performed by converting the SF-36 to SF-6D QALYs to compare QALYs, as well as other sensitivity analyses as recommended by CHEERS.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee and is guided by a Data Safety and Monitoring Board and South Eastern Sydney Local Health District Human Research Ethics Executive (HREC15/331) Protocol version 3, 67 April 2016. Any changes to the protocol are reported to this committee.

Data monitoring

A data safety and monitoring committee (DSMC) will meet after the first 10 participants have been randomised to evaluate study conduct and safety. The DSMC will consist of the principal investigator (non-voting), a interventional radiologist, neurosurgeon, rheumatologist, and general physician. Adverse event monitoring and withdrawal of participants are discussed. The DSMC will meet every 4 months. The DSMC will be provided blinded data but unblinded data can be provided for a specific participant if requested by the committee. If requested it will be provided by an investigator who holds the randomisation schedule.

Harms

CT fluoroscopy guided transforaminal lumbar epidural steroid (1 ml) and local anaesthetic (1ml) is used in the management of sciatica of all durations. The risks associated with this procedure include:

Dural puncture: the needle penetrates into the sac encasing the nerves within the spinal canal, causing leakage of fluid contained within the sac, known as CSF (cerebrospinal fluid). The risk of this procedure is approximately 1% and is treated with flat bed rest for four hours.

Infection: most of these are minor (1-2%), however can be serious (<0.1%) requiring hospital admission, intravenous antibiotics and surgery.

Bleeding: this is rare although more common in patients with bleeding disorders and on "blood thinning" medication. Patients who cannot cease their medications will be excluded from the study (e.g. patients with mechanical heart valve, recent deep venous thrombosis and pulmonary embolus, recent cardiac stent). Otherwise, patients on warfarin have an INR and depending on the value will be asked to cease the warfarin 5 days prior to the procedure and an INR will be checked the day before the procedure and the value must be <1.5. Pradaxa (dabigatran) must be ceased 3 days prior to the procedure, aspirin and platelet inhibitors (plavix, iscover, ticlopidine, persantin) ceased 7 days prior to the procedure, clexane cease 24 hours prior to the procedure. NSAIDs and COX2 inhibitors do not need to be ceased.

Nerve damage: from direct needle trauma, or as a consequence of the above mentioned complications is rare.

Stroke and spinal cord injury: Most of the reported serious complications result from inadvertently injecting steroids with particulate matter into blood vessels close to the injection site, which can lead to brain or spinal cord injury. The risk of stroke or spinal cord damage from a transforaminal epidural steroid injection in the back is quite low when done under CT fluoroscopy.

The risks of high dose short term oral corticosteroids are more common (10-20%) and include insomnia, nervousness, increased appetite, indigestion, headache. There are risks in patients with active peptic ulcer disease of perforation, worsening hypertension in patients with severe hypertension, and hyperglycemia in patients with poorly controlled diabetes or on insulin treatment. These patients are excluded from the trial. Patients who are on diet or oral hypoglycemic medications will be monitored with blood tests to minimise risk of significant hyperglycemia. However, these symptoms and abnormal blood tests will cease with stopping of treatment. There is no risk of suddenly stopping dexamethasone in this study as it is only being administered for 2 weeks.

It is important that women participating in this study are not pregnant or lactating as the study CT scan fluoroscopy radiation, although small, is not zero, and dexamethasone is secreted in breast milk.

An adverse event is any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable or unintended sign, symptom or condition and/or an observation that may or may not be related to the study treatment. A serious adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalization or prolongation

of existing hospitalization, persistent or significant disability/incapacity or congenital/birth defect, condition requiring unnecessary medical or surgical intervention. Solicited reporting of adverse events occurs Days 1 to 7, Weeks 3, 6, 12, 24, 48. Participants can also contact study investigators at any time if they have any concerns. All adverse events are reported to the principal investigator and all serious adverse events are reported to the DMSC and Human Research Ethics Committee.

Auditing
A study meeting to audit trial conduct occurs fortnightly. There is no independent trial audit other than that provided by the DSMC and that required by the Human Research Ethics Committee.

Access to Data and Dissemination
The investigators have access to the final trial dataset. There are no contractual agreements limiting access. Study results of this trial will be submitted for publication in a peer-reviewed journal. Individual level data will be made available after the findings of the study have been published. This data can be used for IPD meta-analyses or for further exploratory research. To obtain this data please contact Marissa Lassere.
The trial is registered on ClinicalTrials. Gov - NCT03240783

Patient and Public Involvement
Patients and or public were not formally involved in the in the development of the research question and outcome measures. Patients were not involved in the design of this feasibility study. Patients were not involved in the recruitment to and conduct of this feasibility study. At the end of the study a report of the study results will be provided to all study participants. In this feasibility study of a randomised controlled trial the burden of the intervention was not assessed by patients or the public.

However, the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586), which includes members of the public, assisted with the design and content of the Patient Information and Consent Form that was developed for this study. As a result of the committee's contribution, the revised Patient Information and Consent Form clearly provides the reason for undertaking the study, the outcome measures involved, explains the nature of the interventions and their burden, and clearly summarises overall study conduct.

ACKNOWLEDGEMENTS
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COMPETING INTERESTS STATEMENT
There are no competing interests.

AUTHORS' CONTRIBUTION
Marissa Lassere conceived and designed the study. Marissa Lassere and Kent Johnson wrote the first draft of the protocol. Peter Smerdely, Grant Pickard and Jeanette Thom critically reviewed the protocol for important intellectual content and approved the final version.

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The sponsor had no role in the study design of this protocol and will have no role in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, or authority over any of these activities.

FIGURE LEGEND

Figure 1. Study Flow Chart

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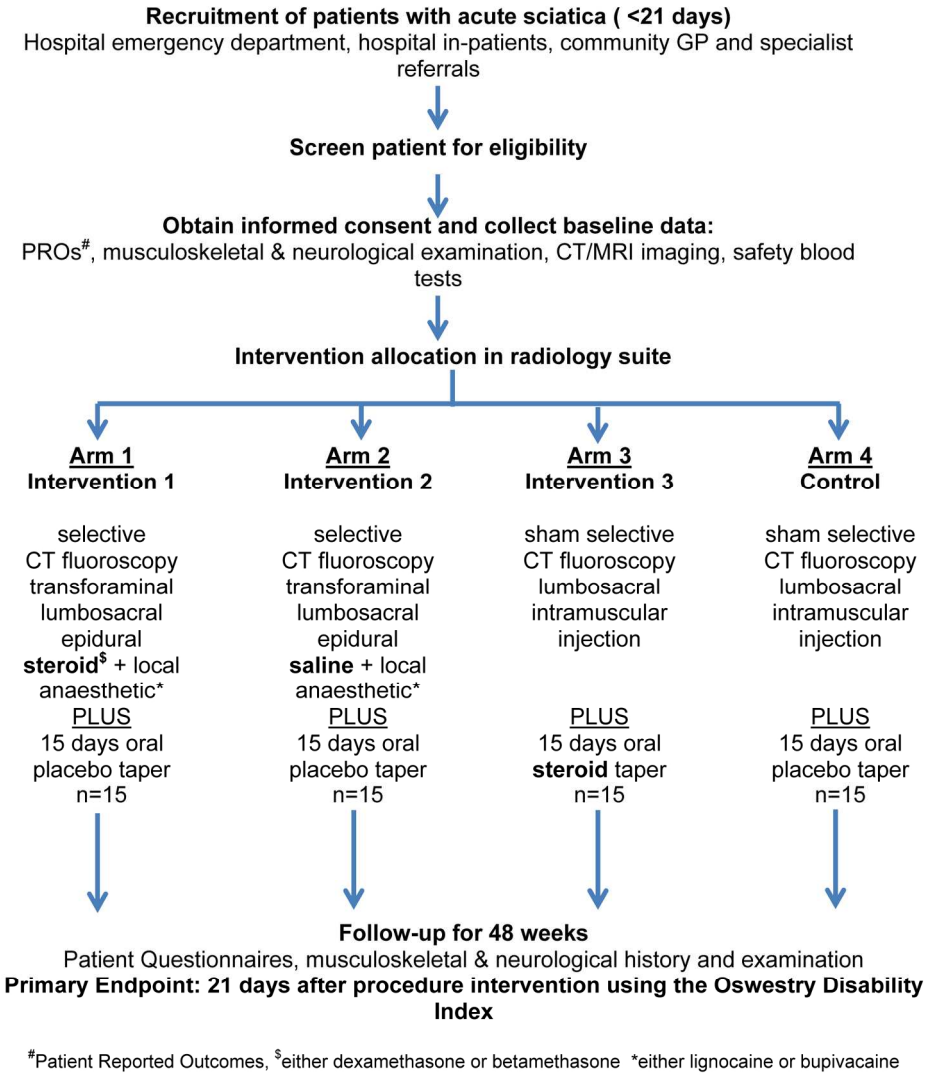

Figure 1. Study Flow Chart

171x184mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4, 7-8
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12,13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17,18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10,11,15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In HREC protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	approved
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	IN HREC protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In patient consent/HREC documentation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	None used
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	HREC
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

BMJ Open

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Title Page

Protocol of the Randomised Placebo Controlled Pilot Trial of the Management of Acute Sciatica (SCIATICA): A Feasibility Study

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ABSTRACT

Introduction: Acute sciatica (symptom duration less than 4 weeks), a major cause of pain and disability, is a common presentation to medical practices and hospital emergency departments. Selective computed tomography (CT) fluoroscopy transforaminal epidural steroid injection (TESI) is often used with the hope of reducing pain and improving function. Recently, there has been interest in using systemic corticosteroids in acute sciatica. However, there is limited evidence to inform management of selective CT fluoroscopy transforaminal epidural steroid in subacute and chronic sciatica and there is no evidence in acute sciatica, even though the practice is widespread. There is also limited evidence for the use of systemic corticosteroids in acute sciatica. Furthermore, the management of selective CT fluoroscopy transforaminal epidural steroid versus systemic steroids has never been directly studied.

Methods and Analysis: SCIATICA is a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of undertaking a blinded 4-arm randomised controlled intervention study of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of interventions. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. Secondary outcome is the ODI at 48 weeks. Other outcomes include numerical rating scale for leg pain, Pain Detect Questionnaire, quality of life, medication use, rescue procedures or surgery, and adverse events. Results of outcomes from this RCT will be used to determine the feasibility, sample size and power calculations for a large multicenter study.

Ethics and dissemination: The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586). ClinicalTrials.Gov NCT03240783

STRENGTHS AND LIMITATION OF THIS STUDY

- In the setting of acute sciatica (less than 4 weeks duration), this 4-arm trial evaluates the feasibility of undertaking a head-to-head route versus pharmacology of intervention randomised controlled trial by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline, and includes blinding with both oral placebo and sham injection across each arm. Such a trial directly provides risk versus benefit of interventions of interest.
- Evaluates feasibility of recruiting and protocol adherence of participants from different referral and demographic settings: public hospital inpatients, private hospital inpatients, emergency department presentations and general practitioner visits.
- Evaluates the challenge of recruiting participants to a RCT of acute sciatica where there often is an expectation of treatment benefit of a procedural intervention by health care professionals (and patients given frequent use of the internet for health care advice), because of a large placebo effect, the natural history of the condition, and extrapolation of results from case series or RCTs with different inclusion criteria, but where there is no direct RCT evidence of benefit and risk .

INTRODUCTION

The colloquial definition of sciatica is pain in the buttock and leg and it is a term understood by the nonprofessional population. The anatomic pathology is usually caused by lumbosacral disc herniation and degenerative lumbosacral spondylosis involving the L2/3 to L5/S1 intervertebral discs and foramina.[1] Therefore sciatica can be associated with numbness, paraesthesia and weakness in the leg. The terms radicular pain and radiculopathy describe this neurological component of the pathology by health-care professionals and researchers.[2] Radicular pain is thought to arise from ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots from ischaemia or inflammation.[3] Radiculopathy indicates that there is conduction block of the spinal nerve or its roots from either mechanical compression or ischaemia. Nonetheless, the terms are still used interchangeably and inconsistently in the randomised controlled trial (RCT) literature.[4],[5] This study defines the term sciatica as radicular pain with or without radiculopathy from lumbosacral nerve root pathology. The definition of acute sciatica in the RCT and systematic review literature also differs. It has been defined as less than 4 weeks, less than 6 weeks and less than 12 weeks duration. Subacute sciatica is usually between 6-12 weeks duration. Chronic sciatica is greater than 12 weeks duration. In this protocol symptoms less than 4 weeks duration are defined as acute.

The prevalence of lumbosacral radiculopathy has been estimated at 3% to 5%[6], whereas referred leg pain is much higher.[4] In an inception cohort of 1,172 patients with acute low back pain presenting to primary care settings in Australia, 25% had leg pain[7]. The majority of participants (72%) with acute sciatica recover completely by 12 months[7]. In another study, 50% of patients with acute sciatica recovered within 4 weeks. However, 30% had persistent leg pain and disability at 12 months[8].

Patients with acute sciatica are treated with a combination of paracetamol, opiate analgesia, non-steroidal anti-inflammatory drugs (NSAIDs)[9-11] pregabalin, and physiotherapy although a systematic review of pharmacologic therapy that included NSAIDs, opioid analgesics, antidepressants, anticonvulsants, muscle relaxants, and opioid analgesics, showed no effect or only small effects in acute, subacute and chronic sciatica[12]. Neuropathic symptom modifiers such as pregabalin have also recently been shown to be ineffective[13].

During the 1970s, failure of conservative management in sciatica and the desire to avoid surgery led to interventional procedures, including epidural steroid injections (ESI). There are three approaches for epidural steroid injections: caudal, interlaminar and transforaminal. The transforaminal approach deposits steroid directly near the ventral epidural space at the affected unilateral nerve root level. Evidence for the superiority of the selective transforaminal approach versus the caudal and interlaminar is generally indirect[14] as there are few high quality head-to-head studies[15]. Selective fluoroscopy (with or without computed tomography (CT) guided fluoroscopy) transforaminal epidural steroid injection (TESI) with local anaesthetic, colloquially described as a "spinal perineural steroid injection", is increasingly being used in the management of patients with acute sciatica in hospital and community settings in the absence of any RCTs undertaken to evaluate the benefit of this procedure in patients with acute sciatica. There are no Cochrane reviews on the management of acute sciatica with epidural steroids of any route[16]. In reviews of epidural steroid injections (caudal, laminar or transforaminal) in sciatica of any duration, not surprisingly, given the heterogeneity of patient populations, interventions, study design and study conduct, conclusions vary considerably. Two recent meta-analyses of epidural steroids in subacute and chronic sciatica [17],[14] conclude that treatment effects are small and of only short duration.

The first transforaminal approach RCT was published in 2000[18]. Five RCTs have been published[19-23] that have had low risk of bias from random sequence generation and participant and personnel blinding. These RCTs show considerable heterogeneity in study design. All RCTs

except one required a symptom duration of at least 4 weeks prior to recruitment. No RCT used CT fluoroscopy. All but one RCT required magnetic resonance imaging (MRI) evidence of disc herniation[18] . Two studies excluded patients with evidence of foraminal stenosis [21 23]. Three studies did not report neurological features.[20],[22],[23] All studies included an epidural control, but only one study also included a non-epidural control[21]. Only two studies clearly specified the primary endpoint[21],[22], but these two studies had incomplete follow-up as they did not obtain further data on patients who failed to achieve a 50% reduction of pain 4 weeks after the last procedure. Where epidural saline was used as an epidural control, speculated mechanisms for a therapeutic effect include washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.[21],

Harms have been reported with transforaminal epidural steroid injections[24] including infection and bleeding. In 2014, the Food and Drug Administration (FDA) issued a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including "loss of vision, stroke, paralysis, and death." [25]. The risk is greater for particulate versus non-particulate steroids and in cervical versus lumbosacral epidurals. Recently a consensus opinion paper was published on safeguards to prevent neurologic complications after epidural steroid injections[26]. The clinical considerations were based on conventional fluoroscopy with contrast and not with CT fluoroscopy. RCTs show no difference in efficacy between particulate and non-particulate steroids[27-29].

Unlike epidural steroids, systemic steroids have been studied in acute as well as subacute sciatica. A meta-analysis of 7 small of studies of variable quality of intramuscular (IM), intravenous (IV) and oral steroids found steroids were not superior to placebo and had more adverse events[30]. Adverse events, however, were clearly related to the very high dose of dexamethasone used in 3 of the 7 studies (120 mg of dexamethasone in 3 days which is the equivalent of 800mg of oral prednisone). In another systematic review[12] three studies of acute sciatica using smaller doses of steroid, a significant effect on short-term overall pain and leg pain was found. A RCT of IM steroid versus IM saline failed to show a difference in leg pain scores[21]. A blinded RCT reported that IV dexamethasone (8mg) improved pain scores at 24 hours and reduced ED length of stay compared to placebo. There was no difference at 6 weeks[31]. No CT/MRI imaging evidence was required. A recent blinded RCT of patients of oral steroids (prednisone 60mg 5 days, 40mg 5 days and 20mg 5 days) with sciatica less than 12 weeks duration showed an improvement in function at 3 weeks and 52 weeks but no improvement in pain[32].

In summary, there are two issues that are relevant that provides the rationale for this pilot/feasibility study (i) the condition under study i.e. acute, subacute or chronic sciatica, (ii) the route of interventional procedure (caudal, interlaminar and fluoroscopic transforaminal epidural (the last with or without CT guidance) or systemic route. There are no RCTs in acute sciatica published using steroid epidurals of any type. There are RCTs in acute sciatica with systemic steroids. In subacute and chronic sciatica there are no RCTs that have used selective CT fluoroscopy transformational steroid injection, indicative of the fast pace of changing technological procedural interventions without RCT evidence. Arguably, steroids may be more effective for sciatica when provided in the acute setting, but this should be subjected to rigorous evaluation. In Australia selective transforaminal epidural steroids is guided by computed tomography (CT) fluoroscopy, therefore is performed by interventional radiologists. Given their use and perceived effectiveness, and the costs and potential harms associated with their use, there is an identified need to properly evaluate the use of epidural and systemic steroids in acute sciatica in adequately controlled trial designs with a control arm for the route of procedure. Furthermore, given that there is a rationale for the benefit of epidural saline in acute sciatica, epidural steroid could be directly compared to epidural saline to evaluate pharmacology versus a simple physical washout of inflammatory cytokines, lysis of inflammatory mediated adhesions and enhanced blood flow to ischaemic nerves.

There is a clear advantage of directly comparing different interventions in a single randomised control trial. These advantages include improving internal validity, marginally reducing sample size, and limiting heterogeneity by standardising assessments and conduct procedures. However, there are also disadvantages such as longer time to trial recruitment, therefore longer time to trial completion, more exclusion criteria because of differing interventions, and difficulty explaining design to participants.

METHODS / ANALYSIS

Study Objectives

Primary objective

Undertake a pilot/feasibility study of patients with acute sciatica designed to evaluate the feasibility of a blinded 4-arm RCT of (i) selective CT fluoroscopy transforaminal epidural steroid (Arm 1), (ii) selective CT fluoroscopy transforaminal epidural saline (Arm 2), (iii) 15 days of a tapering dose of oral steroids (Arm 3), and (iv) a sham epidural and oral placebo control (Arm 4). This feasibility study is designed to evaluate head-to-head, route versus pharmacology of corticosteroid intervention by comparing epidural steroid with systemic steroids, and epidural steroid with epidural saline and includes blinding with oral placebo and sham injection across all arms. The primary outcome measure is the Oswestry Disability Index (ODI) at 3weeks. The primary analysis is comparison of CT fluoroscopy guided transforaminal lumbar epidural steroid versus sham injection (Arm 1 versus Arm 4 in Figure 1. Study Design).

The pilot/feasibility study will evaluate the following issues: rate of recruitment, study conduct including randomisation allocation concealment, preparation of interventions, choice of procedural corticosteroid and local anaesthetic, blinding, efficient organisation of initial assessments, diagnostic imaging, and ensuring efficient study processes across public/private hospital inpatients, emergency department /room (ED/R) presentations and general practice visits, and timeliness of providing the intervention within the 4 week acute sciatica requirement. Rate of recruitment is important particularly where there already is an expectation of treatment benefit “spinal perineural steroid injections” by health care professionals and patients.

This pilot/ feasibility study is a single centre Human Research Ethics Committee (HREC) study, but includes recruitment from multiple sources and the interventions will be delivered in public hospital, private hospital and community radiology practices. The recruitment of participants and the delivery of the interventions have been designed to identify feasibility issues given these different settings.

Secondary objectives

1. Obtain preliminary results from this RCT which will be used to calculate the sample size and power calculations for a full-scale study of treatments currently used in the management of acute lumbosacral radiculopathy of less than 4 weeks duration is the most effective in reducing pain and disability in the short-term and prevent progression to persistent or recurrent lumbosacral radiculopathy in the long term.
2. Evaluate the adequacy of outcome measures in acute sciatica, where pain, sensory and motor neurological symptoms all cause distress and disability, and where pain caused by nerve root irritation often progresses to loss of pain and may be replaced by sensory loss or weakness from nerve root conduction impairment. The importance of describing this multifactorial pathology and how it impacts the primary endpoint, the Oswestry Disability Index has substantive importance regarding the optimal primary and secondary endpoint for use in a full-scale RCT. Other outcome measures will also be evaluated such as confounding by medication use and taper, protocol compliance and burden, confounding by modification of activities and need and timing of rescue procedures.

3. Although this is a feasibility study, for transparency the following are the pre-specified hypotheses for powering a full-scale RCT. In patients with acute sciatica, selective CT fluoroscopy transforaminal lumbar epidural steroid (Arm 1) is (a) superior to control (Arm 4) and (b) non-inferior to a 15 day tapering dose of oral dexamethasone (Arm 3) in reducing short-term pain and disability (after 3 weeks) as determined by the Oswestry Disability Index. Further information regarding hypotheses and sample size is described in the sample size section.

Participants, interventions and outcomes

The study setting is the rheumatology service at a large teaching hospital in Sydney, Australia. The teaching hospital services a population of about 1 million of Southern Sydney. The eligibility criteria are as follows:

Inclusion criteria

(i) leg pain of any description with clinical findings consistent with single level radiculopathy,
(ii) minimum symptom duration > 72hrs,
(iii) maximum symptom duration < 3 weeks to ensure symptom duration at randomisation is < 4 weeks,
(iv) no previous episode of same level radicular pain in the previous 6 months,
(v) pain intensity at >30 on the Oswestry Disability Index (ODI),
(vi) imaging (MRI and/or CT) indicating herniated disc or foraminal stenosis or both, concordant with the level indicated by history and physical examination,
(vii) age at least 18 years

Exclusion criteria

(i) previous transforaminal epidural steroids at any level in the last 12 months,
(ii) previous oral steroids in the last 12 months,
(iii) any lumbar surgery at same level, or above or below the level at any time,
(iv) previous lumbar surgery at any other level to that in (iii) within the last 12 months,
(v) pregnancy, or lactation/breastfeeding
(vi) direct indication for neurosurgery (e.g. cauda equina syndrome, or progressive motor loss i.e. ≤ 3/5 power),
(vii) inability to read or understand English
(viii) any serious medical or psychiatric condition that may interfere with participation or outcome assessment such as: need for uninterrupted anti-coagulation, spinal fracture, active infection or metastatic disease suspected, active cancer, poorly controlled diabetes, or patients with diabetes on any insulin, uncontrolled hypertension (systolic blood pressure >180 or diastolic blood pressure >110 within 30 days of randomization date), active peptic ulcer disease, history of intolerance to steroid therapy, previous or current psychiatric history of bipolar disease, or secondary gain such as anticipated or ongoing legal proceedings, history of substance abuse
(ix) no other pathology likely to explain condition (e.g Guillain-Barre Syndrome, vasculitis)

Both MRI and CT scan are acceptable for entry criteria. If CT is equivocal regarding pathology or level, then the patient will proceed to MRI, or the patient is not included in the study. Scans are performed without contrast. All potential participants will be reviewed by a study physician (rheumatologist) who will undertake a history and physical general, musculoskeletal and neurological examination to ensure inclusion and exclusion criteria and exclude 'red flags' and alternate diagnoses. Full laboratory examination of safety includes full blood count (FBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), coagulation profile, electrolytes, urea, creatinine (EUC), liver function tests (LFTs), fasting blood glucose. Patients who can cease

antiplatelet and anticoagulant medications safely will be given instructions on how to do so, or are excluded. The CT and/or MRI images are reported by an experienced radiologist who is unaware of the study, and the results are discussed with the participant and their treating physician. If the report is unclear, the images are reviewed by an independent radiologist at a radiology meeting to clarify imaging pathology. If imaging pathology remains unclear then eligibility is not met. The images are also reviewed by the interventional radiologist prior to the procedure (see Implementation). If the interventional radiologist cannot confirm the specified imaging pathology the procedure is aborted and the principal investigator is contacted.

Interventions

The interventions are as follows and also summarised in Table 1 and Figure 1.

Procedural interventions. Once the specific spinal nerve pathology has been selected clinically and on imaging (e.g. right S1 nerve root at L5/S1 intervertebral space), all participants are given an injection of local anaesthetic (lignocaine or bupivacaine) into the skin and subcutaneous tissue at this selected site.

Participants in Arm 1 will receive selective CT fluoroscopy transforaminal epidural dexamethasone 4mg (1ml) a non-particulate corticosteroid with the local anaesthetic lignocaine 1% (1ml). However, if participants are an inpatient at St George Hospital they will receive betamethasone (1ml) as celestone chondrose 5.7mg/ml, a particulate corticosteroid with the local anaesthetic bupivacaine 0.5% (1ml). This is at the direction of two interventional radiology investigators who have differing preferences regarding procedural agents. The interventional radiologist and their preference is known and will be addressed in the hierarchical linear model analysis.

Participants in Arm 2 will receive selective CT fluoroscopy transforaminal epidural 0.9% normal saline (1ml) and lignocaine 1% (1 ml) unless they are hospital inpatients in which case they will receive bupivacaine 0.5% as the local anaesthetic agent. The saline epidural has two purposes in this pilot/feasibility study. There is no consensus in the literature regarding the optimal control for the evaluation of epidural steroids [33]. Moreover, there is some evidence that it has a therapeutic effect[21]. Therefore this pilot/feasibility study is designed to explore these issues by including both epidural saline arm (Arm 2) and a sham injection (Arms 3 and 4).

Participants in Arms 3 and Arms 4 will receive sham selective CT fluoroscopy intramuscular injection with needle placement down to muscle layer and no injection of any fluid. The intervention is performed by an experienced interventional radiologist. The intervention radiologist is not blind to the procedure (see section Blinding, for more information).

Oral intervention. The oral steroid is dexamethasone. The 15 day taper dosing is (i) 4 mg at 8am and 6pm days 1-5, (ii) 2 mg 8am and 6pm days 6-10, and (iii) 1mg 8am and 6pm days 11-15. Dexamethasone has a longer biological half-life than prednisolone. The oral interventions are over-encapsulated in gelatine capsules packed with sucrose and lactose. The placebo is sucrose and lactose only. Participants in Arm 3 receive the oral dexamethasone capsules, and participants in Arms 1, 2 and 4 receive the placebo capsules. Dexamethasone and placebo capsules have identical appearance and are prepared by a compounding pharmacist. The capsules are placed in three plastic bottles with clearly labelled instructions. At each telephone or in-person contact treatment adherence is monitored.

Concomitant management and interventions: All participants have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. All concomitant therapy will be recorded at each visit. Rescue therapy includes CT fluoroscopy transforaminal epidural of steroid and neurosurgery.

Table 1: Summary of the experimental interventions by Arm

Arm	Experimental intervention
Arm 1 **Intervention 1** Injectable Dexamethasone and Lignocaine OR Betamethasone and Bupivacaine selective CT fluoroscopy guided transforaminal lumbar epidural steroid	**Drug: Betamethasone OR Dexamethasone Injectable** Procedural agents. The steroid and local anaesthetic preparation is determined by interventional radiologist's preferences regarding the use of particulate or n on-particulate steroids. Dexamethasone 4mg (1ml) is a non-particulate corticosteroid and is used with the local anaesthetic lignocaine 1% (1ml). Betamethasone Sodium Phosphate/Acetate 5.7 mg/ml Injectable is a particulate corticosteroid and is used with the local anaesthetic bupivacaine 0.5% (1ml). Other Name: celestone chondrase 5.7 mg/ml injectable suspension Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 2 **Intervention 2** Normal Saline Flush, 0.9% Injectable Solution with either Bupivacaine or Lignocaine selective CT fluoroscopy guided transforaminal lumbar epidural normal saline	**Drug: Normal Saline Flush, 0.9% Injectable Solution** Procedural agents. The local anaesthetic preparation used with the Normal Saline Flush, 0.9% Injectable Solution, will be standardized to replicate current radiology interventional practices: either local anaesthetic bupivacaine 0.5% (1ml) or local anaesthetic lignocaine 1% (1ml). Other: Sham injection and/or oral placebo The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 3 **Intervention 3** Dexamethasone oral capsule 15 day tapered dosing as follows: (i) days 1-5, 4 mg morning and evening, (ii) days 6-10, 2 mg morning and evening, and (iii) days 11-15, 1mg morning and evening.	**Drug: Dexamethasone Oral Tablet** Dexamethasone Oral Tablet: 15 day taper dosing is: days 1-5 8mg (4mg morning and evening) , days 6-10 4 mg (2mg morning and evening), and days 11-15 2 mg (1mg morning and evening). The dexamethasone is over-encapsulated in a gelatine capsule that is identical to the placebo capsule in appearance. Other: Sham injection and/or oral placebo The sham Injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.
Arm 4 **Control** Sham injection and/or oral placebo: CT/ fluoroscopy guided (parameters set to zero) transforaminal lumbar sham (needle placement down to muscle and no injection of any fluid) AND	**Sham Injection and/or oral placebo** The sham injection procedure is needle placement down to muscle at the designated spinal level and no injection of any fluid. The oral placebo is a gelatine capsule packed with filler.

placebo oral tablets taper.	

Outcomes

A recent publication on core outcomes domains for clinical trials in non-specific low back pain recommended physical functioning, pain intensity, and health-related quality of life [34].

Primary outcome measure.

The Oswestry Disability Index (ODI) version 2.0 [35] is the primary outcome measure. The ODI is a functional status measure specifically developed for disorders of the spine and has been used in most RCTs of sciatica[36] and see Table 2. It is a 10-domain 2-page 5 minute questionnaire with ordered 6-response-item (0-5) scales for each question. The questions address domains of pain, physical functioning, sleeping, home/work functioning and impact on social life. The scores are summed, then doubled and the final score is 0-100. The ODI will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48. This will be administered at visits, phone or mail. The primary analysis is the short-term outcome, reduction of disability at 3 weeks on the ODI. The secondary analysis is the long-term outcome, reduction of disability at 48 weeks on the ODI.

Secondary outcomes.

Numerical Rating Scale (NRS) for leg pain is the main secondary outcome. A measure of leg pain is included in all studies of sciatica. The NRS is a validated[37] 11 point scale. Participants will be asked to rate their average leg pain over the preceding 24 hours. Zero represents 'no leg pain' and 10 represents 'worst imaginable pain'. Although the Visual Analogue Scale (VAS) is a more frequently included measure, unlike the VAS, the NRS can be verbally administered by phone. This will be administered at Eligibility Baseline/Randomisation (day 0), day 1-7, weeks 2, 3, 6, 12, 24, 48.

Numerical Rating Scale (NRS) for back pain. The severity of back pain may differ to that of leg pain so both measures are needed. It is rated as an average over the preceding 24 hours and will be administered at Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Pain DETECT Questionnaire [38]. At Eligibility Baseline/Randomisation (day 0), day 1- 7, weeks 2, 3, 6, 12, 24, 48.

Short-Form 36 (SF-36) questionnaire [39] evaluates health related quality of life and will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48.

Lumbosacral and lower limb musculoskeletal and neurological history and clinical examination at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. This includes inspection of gait, lumbosacral spine and lower limbs for scoliosis, asymmetry, loss of lumbar lordosis, abnormal gait and stance, weakness, muscle wasting, muscle fasciculation, palpation of lumbosacral spine for tenderness and rigidity, movement of lumbosacral spine in flexion and extension, hip, knee and ankle range of movement, straight leg raise and femoral stretch test. Neurological examination of lower limb includes further inspection, examination for tone (normal, increased, decreased), clonus (present absent and beats of clonus if present), power (0, 1, 2, 3, 4, 4+ and 5 out of 5) for 12 lower limb movements (hip abduction, adduction, flexion, extension, knee flexion and extension, ankle dorsiflexion, plantar flexion, inversion and eversion, big toe extension and flexion) , knee and ankle reflexes (increased, normal, decreased absent), plantar reflexes (normal, up-going, equivocal, no response), and pinprick, light touch, proprioception and vibration sensory examination.

Work and health utilisation measures at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. These will include days missed from paid employment (if applicable) because of sciatica, use of health services such as doctor, other health-care provider related visits (e.g. acupuncture, chiropractic), injection procedures and neurosurgery. This information will be obtained by interview at each visit and is documented in the case report form developed for the study.

Demographic and socioeconomic measures measured at baseline include age, gender, and occupation/previous occupation.
Imaging findings on CT and /or MRI will be used to define the site, level, type and degree of pathology using classification systems for disc herniation [40] and severity of nerve root compression [41]. This data will be used to determine imaging predictors of response.
Medications: use of all other medications including analgesics, NSAIDs, opiates, gabapentin and pregabalin will be documented at every visit.

Economic evaluation: Outcomes for an economic evaluation will also be collected in this feasibility study. The feasibility of a cost-effectiveness analysis will be undertaken using the ODI and a cost-utility analysis [42] using the EQ5D-5L for incremental costs per quality-adjusted-life-year (QALY)[43]. The EQ5D-5L questionnaire will be administered at Eligibility, Baseline/Randomisation (day 0), day 1, day 7, weeks 3, 6, 12, 24, 48. Work and health utilisation measures described above will also be collected. Costs within each randomised arm will be assessed in terms of hospital, health care visits, investigations, such as CT and MRI imaging, procedure costs and medications costs. These direct costs are determined with Diagnosis Related Groups cost weights for hospital in-patients, and for outpatients by the Australian Medical Benefits Scheme standard fees, and the Australian Pharmaceutical Benefits Scheme (PBS). These costs are determined by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) Manual of Resources items and their associated costs used for economic analyses[44], [45]. The PBAC does not require questionnaires of productivity[44],[45] such as the PRODISQ[46] and similar questionnaires of resource utilization.[47]
Adverse events will be collected at day 1, day 7, weeks 3, 6, 12, 24, 48. These will include steroid adverse effects (blood pressure, blood glucose, changes in mood and sleep) and procedural adverse effects (headaches, bleeding) and information about additional procedures, surgery and hospitalisations.

Table 2: Schedule of enrolment, interventions and assessments

	STUDY PERIOD											
	Screening& Eligibility	**Allocation**	**Post allocation**									**Close-out**
TIMEPOINT	-T1	0	T1	T2	T3		T4	T5	T6	T7	T8	T9
D=Day W=Week		**D0**	**D1**	**D 2-6**	**D7**	**D 8-15**	**D14**	**D21**	**W6**	**W12**	**W24**	**W48**
ENROLMENT												
Eligibility Screen	✓	✓										
Neurological and musculoskeletal Examination	✓	✓										
Safety Blood Tests	✓	✓	✓		✓			✓				
MRI (or CT if MRI contraindicated or CT clearly demonstrates imaging pathology)	✓											
Oswestry Disability Index	✓	✓										
Informed Consent	✓											
Allocation		✓										
INTERVENTIONS												
Procedural injection in radiology suite		X										
Oral medications		X	X	XXXX	X	XXXX XXXX						
ASSESSMENTS												
Outcome Variables												
Oswestry Disability Index	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Numerical Pain Rating Scales	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
PAIN DETECT Questionnaire	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
SF-36	✓	✓			✓		✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Work/health utilisation/costs	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Medication History	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Neurological and musculoskeletal Examination			✓		✓			✓	✓	✓	✓	✓
Safety Blood Tests			✓		✓							
Other Data variables												
Rescue procedure history			✓		✓			✓	✓	✓	✓	✓
Participation Randomization perception			✓		✓			✓	✓	✓	✓	✓
Adverse Events & Serious Adverse Event Assessment		✓	✓	✓	✓			✓	✓	✓	✓	✓

Sample size

Most trials of subacute and chronic sciatica of a selective CT fluoroscopy transforaminal epidural steroid injection have a sample size of 30 participants per arm. The primary outcome in this pilot/feasibility study is the ODI at 3 weeks comparing epidural steroid and sham injection (Arm 1 vs. Arm 4). With 15 participants per arm, there is 85% power to detect a difference of 17 ODI points between these two arms, given a standard deviation of change of ODI of 15.1 points[32]. Statistical test on which calculation is based is the independent two-sample t-test with a two-tailed alpha of 0.05 (Stata 14). This is a total of 60 participants in this pilot/feasibility study. This is sufficient to evaluate feasibility of the study design, study conduct and determine sample size for a full-scale multicentre study. However, this ODI difference is a large unrealistic effect. The minimum clinically important difference in ODI scores in one study was 7.0 points [48], and an international consensus group found empirical evidence of 4 to 15 ODI points[49] and recommended a cutoff value of 10 ODI points. Given that we are recruiting participants with acute sciatica of less than 4 weeks duration, an ODI difference of at least 10 ODI points is very reasonable. A sample size of 49 participants per arm will provide 90% power to detect a minimum clinically important difference of 10 ODI points assuming a standard deviation of 15.1 with a two-tailed alpha of 0.05 (Stata 14). Allowing for 20% dropout (which at 3 weeks is unlikely but at 48 weeks is more likely), 236 participants will be recruited, 59 to each arm. Although there are 6 possible comparisons in a 4 arm trial, controlling for type-1 error rate is not needed when several different experimental arms are compared with the control[50],[51]. Therefore no multiplicity adjustment is needed for: (i) Comparison I- Arm 1 versus Arm 4 (epidural steroid is superior to control), (ii) Comparison II - Arm 2 versus Arm 4 (epidural saline is superior to control), and Comparison III - Arm 3 versus Arm 4 (oral steroid is superior to control). However, in order to proceed to Comparison IV, Arm 1 versus Arm 3 (epidural steroid is superior to oral steroids), we must first demonstrate that Comparisons I and III were statistical significant, and there must be a type-1 error consideration[52]. Furthermore, if the hypothesis is that oral steroid is non-inferior to epidural steroids, then the ignorable difference must also be prespecified. The pilot/feasibility study will provide data that will be helpful in determining these sample size calculations. The feasibility study will be informative regarding the estimated mean difference in this population, its standard deviation, and pattern of missing data at each of the study visits.

Recruitment processes

Participants will be recruited from (i) Emergency departments (EDs) of public hospitals, (ii) current inpatients of public and private hospitals and (iii) referral from community general practitioner or medical specialist (rheumatologist, neurosurgeon or orthopaedic surgeon) from the Sydney metropolitan area around St George Hospital. It is anticipated that the majority of participants will be recruited from emergency department presentations and general practitioners. Participants with sciatica symptoms less than 21 days duration are screened so that participants can be evaluated and undergo the allocated intervention within the 4 weeks eligibility criteria.

St George Hospital Emergency Department, as well GPs and relevant specialists in the geographic area (population approximately 270,000) serviced by this hospital area have been provided information about SCIATICA study, the inclusion/exclusion criteria, explanation of the trial rationale, and the opening of a daily acute sciatica clinic at St George Hospital centre as the portal of entry for trial patients.

Participants presenting to the Emergency Department (ED) with acute sciatica are assessed according to ED's usual procedures and staff admit or discharge patients according to their usual care pathway. If the ED does not admit a potential acute sciatica participant, a study clinician is contacted by phone Monday-Friday 9am to 5pm (business hours) and a referral is faxed. Out of business hours, a referral is faxed to the acute sciatica clinic which is processed the next business

day (see below). All referred participants are given a brochure by the referring ED clinician outlining the study. The acute sciatica clinic is also available for urgent referrals from community general practitioners and specialists. This is by fax or by telephone. These referred participants are also given a brochure by their referring clinician. All referred potential participants are logged. Within 1 to 3 days, Monday to Friday, all referred participants are contacted by telephone by a study clinician and a telephone history is obtained to ascertain suitability regarding inclusion and exclusion criteria. Where eligibility is clear or indeterminate, an eligibility visit is organised within the next couple of days. At this visit a full history and examination, musculoskeletal and neurological is conducted to determine underlying pathology, and if acute sciatica is likely, then lumbosacral imaging preferably with MRI imaging and blood pathology is requested. Patients complete routine clinical practice questionnaires as part of clinic audit including ODI, SF-36 and EQ-5D-5L. Conservative therapy is initiated (medication/physiotherapy) as appropriate. Potential participants are provided with the Participant Information and Consent Form and further information regarding the RCT if eligibility criteria are likely. Once imaging and pathology becomes available the participant is contacted and informed of the results. If s/he meets the criteria s/he is invited to participate in the RCT. At one of the visits prior to randomisation, all participants are reviewed by the principal investigator to ensure that all eligibility criteria are met. This includes a full general, musculoskeletal and neurological history and clinical examination and confirmation of imaging. If eligibility criteria are met and the participant agrees to participate, then the participant proceeds down study pathway. Processes are in place to ensure that enrolees, if they agree to participate, are safely fast-tracked to randomisation and RCT interventions.

If patients do not agree to participate in the RCT they can either decide to continue their management in the acute sciatica clinic, and if their general practitioner is willing then the patient's ongoing management is determined by the rheumatologists who run the acute sciatica clinic. If the patient wishes to be managed by their GP, a letter from the acute sciatica clinic is sent to the GP to facilitate management. The patient has the option of returning to the acute sciatica clinic for further management or advice as needed. A log of potential participants who decline or are ineligible for any reason is kept for later evaluation consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines[53]. Reason for rejection or refusal will be recorded if available as well as age, gender, race/ethnicity and ODI score. If the participant does not wish to participate in the RCT but wish to be managed in the acute sciatica clinic they are included in a clinical audit of the management of acute sciatica. The management is determined in consultation with the patient and is generally conservative therapy unless there is severe pain and progressive functional disability preventing return to work or normal activities, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

The participant may clearly not meet the eligibility criteria at telephone screening. If patient safety is not an urgent consideration, patients who have anticipated or ongoing legal proceedings, need uninterrupted anti-coagulation or active cancer (as exclusion criteria) are not progressed to the eligibility visit but are asked to see or return to their treating doctor. Participants that do not have any leg pain are also asked to see or return to their treating doctor. However, if a referred patient has a history that suggests cauda equina syndrome or symptoms suggestive of malignant or infection-related pathology, the patient is seen urgently in the acute sciatica clinic and appropriate investigations and management are instituted.

If the participant does not wish to participate they are included in a clinical audit of the management of acute sciatica during the admission and the participant is continued to be managed according to the treating clinician. This is generally conservative therapy unless there is progressive severe pain and functional disability preventing discharge, progressive motor weakness, or features on the MRI imaging that suggests that neurosurgical review is needed.

If the participant is admitted to hospital with acute sciatica the admitting team will contact the study investigators. Most patients with acute sciatica in our setting are either admitted under the general medical team, the rheumatology team or the neurosurgical team. The same processes are followed for in-patients as described above for out-patient referrals. Only a study investigator can consent a participant to participate in SCIATICA

All participants are told that participation is voluntary, they can discuss participation with family, friends or their health care practitioners, and if they decide not to participate, it will not affect the treatment they receive now or in the future. They can have family and friends with them during the consent process. They can also withdraw from the study once it has started, at any time without having to give a reason.

Assignment of interventions

Sequentially numbered, opaque and sealed envelopes contain the randomised intervention. Participants are randomly allocated 1:1:1:1 by computer-generated random numbers using permuted blocks stratified by duration of sciatica (≤2 weeks, >2 weeks). The randomisation schedule including details of blocking schedule are held off-site by the randomised allocation sequence study investigator who is not involved in participant recruitment , assignment of interventions or data collection to ensure allocation concealment. This study investigator places the study medications and procedure instructions for each arm in separate opaque sealed envelopes. These two envelopes in turn are placed into a single larger opaque sealed envelope labelled with a sequential number and the randomisation number. The sealed envelopes are held in a locked cabinet until retrieved by the blinded study investigators who are involved in participant recruitment, provision of the study interventions, participant management and data collection. The acute sciatica clinic study investigators are blind to the study intervention.

Implementation of interventions

The day of study intervention implementation, the participant has safety bloods performed, unless eligibility safety bloods had occurred in the previous week. The participant completes the study questionnaires and the study clinician once more ascertains eligibility criteria by history and examination immediately in the morning before attending the radiology suite. If the criteria are still met the study clinician indicates the exact site of the CT fluoroscopy transforaminal epidural on a request form that is provided to the interventional radiologist. For example, “perform a selective CT fluoroscopy transforaminal epidural of corticosteroid and local anaesthetic at L5/S1 targeting the right S1 nerve root”. The MRI images are also provided to the interventional radiologist. The research officer retrieves the next in sequence numbered large opaque labelled sealed envelope. The research officer accompanies the participant, taking the interventional request, images (films or on CD) and large opaque labelled sealed envelope to the radiology suite. At the radiology suite the research officer opens sealed opaque envelope, gives the ‘procedure’ envelope with instructions to the radiologist and exits. The radiologist evaluates the MRI images, then opens the procedure envelope. It contains one of three instructions: (i) selective CT fluoroscopy transforaminal epidural steroid and local anaesthetic injection, (ii) selective CT fluoroscopy transforaminal epidural normal saline and local anaesthetic injection or (iii) intramuscular sham injection down to muscle layer but no injection of any fluid. The side (right or left) and lumbosacral level (e.g L5/S1) is determined by the radiology request form. The participant is positioned prone as per a CT fluoroscopy transforaminal epidural, the CT fluoroscope is positioned as if a CT fluoroscopy transforaminal epidural is performed, local anaesthetic is injected into the skin and subcutaneous tissue. Radiologist and his staff maintain patient blinding. CT/fluoroscopy guided transforaminal lumbar epidural radiation parameters are set to reduce radiation dose. There is no radiation dose for CT/fluoroscopy guided transforaminal lumbar sham injection because the parameters are set to zero although the machine is on. All CT fluoroscopy images are saved for further analysis.

At the end of the procedure once outside the CT fluoroscopy room, the research officer gives the opaque envelope marked "Dexamethasone or placebo capsules" to the participant and explains how the medications are to be taken over the next 15 days. There are three plastic bottles labelled Days 1-5, Days 6-10 and Days 11-15. The participant opens the Day 1 labelled bottle and swallows the capsule. The participant continues to lie flat for at least one hour after the procedure, the participant is forbidden to drive for 24 hours and a person accompanies them home. The interventional radiology procedure report states that the participant had a procedure as part of the SCIATICA RCT and to contact the chief investigator if there is a concern, a phone number is provided.

Masking/Blinding.
All personnel except the radiologist delivering the procedure and the investigator responsible for randomisation and preparing the interventions will be blind to the randomisation arm. The trial participant, study clinicians, research officers, participant's treating care providers, outcome assessors, and data analysts are blind to the intervention assignments. In the event of a serious medical emergency during which the treating doctor must know in which arm the participant was randomised, the randomised code can be broken. Each participant is given a 24 hour emergency contact number and the principal investigator contacts the investigator who holds the randomisation schedule to determine the participants allocated intervention.

Data collection, management and analysis
Data collection methods
Data quality of outcome, baseline and other trial data is safeguarded with standardisation, assessor training and duplication of measurements and assessments by research officers administering the questionnaires and study clinicians undertaking the history and clinical examinations. All assessments are reviewed and the history and clinical findings confirmed by the principal investigator prior final eligibility determination. Study clinicians meet every 2 weeks to discuss ongoing assessments, issues of standardisation, equivocal or unclear findings and or any other concerns. All questionnaire data is scanned, with range checks for data values, and verified. Free text data scanned and verified. Clinical data is coded and verified. Participants' retention and complete follow-up is encouraged through contact by phone or text and visits are organised so that they are maximally convenient for participants. This often requires visits to be conducted at the end of the normal working day.

Data/Statistical Analysis Plan
Although this is a pilot/feasibility study to evaluate several important clinical and trial design considerations the following data analysis plan is proposed for transparency. In this feasibility study treatment is analysed by intention-to-treat and the data analyst will be blind to arm allocation. A two-tailed p-value <0.05 is considered statistical significant. The primary analysis is an analysis of variance evaluating the effects of treatment on the ODI at week 3, using treatment arm, baseline ODI and duration of symptoms in days as covariates. The primary comparison is epidural steroid versus control. However, similar analyses will be applied to the other treatment comparisons with control (epidural saline versus control, oral steroid versus control) without a type-1 error penalty. However, the epidural steroid versus oral steroid comparison will require type-1 error consideration[52]. All comparisons are made at Day 21, where Day 0 is the day of the procedural intervention immediately followed by the first dose of the oral intervention. Day 21 is the 3 week endpoint. Similar analyses will also be applied at the 6 and 48 week endpoints for the ODI.

Multilevel linear mixed model will examine time trend by treatment arm interaction. This linear mixed model will be used to model ODI trajectory across all 10 time-points by treatment arm, where treatment arm is a property of the persons and visit is nested within person. The random-effect portion of the model is time, which here is each measurement, treated in the model as monthly time intervals. Analyses will be undertaken unadjusted and adjusted for (i) medication use,

(ii) presence of a definite motor radiculopathy (iii) days from onset of sciatica pain to delivery of the intervention, (iv) whether the imaging demonstrates a prolapsed disc, a sequestered disc or a extruded disc fragment, (v) whether imaging demonstrates bony/osteophytic narrowing of the neural exit foramen , and (vi) age. Missing data will be handled with multiple imputation, using iterative Markov chain Monte Carlo (MCMC) which requires the assumption that the data are missing at random[54]. An intention to treat analysis with multiple imputation is the primary analysis, however, a completers analysis will also be undertaken as a secondary analysis. The value of undertaking a feasibility study is that patterns and reasons of missing data that are not at random may be identified and in the full-scale study targeted efforts made to reduce this potential bias. There is no interim analysis.

Other outcome measures (NRSs, SF-36, EQ-5D and clinical data measured on a continuous scale) will also be analysed with multilevel mixed effects linear regression. All analyses will be undertaken unadjusted and adjusted for other medication use, type of procedural steroid, presence of neurological signs, and MRI findings with multivariate methods. A full description of neurological signs will be reported in tabular form and descriptive statistics. Safety data will be analysed in reported in tabular form and with descriptive statistics.

Economic Evaluation

This feasibility study will provide data to identify issues conducting an economic evaluation for the full-scale study. The rationale for undertaking an economic evaluation is to evaluate the feasibility of undertaking a pre-specified cost-effectiveness economic evaluation in the full-scale study. In Australia, all drugs and more recently, certain procedures, undergo a cost-effectiveness analysis to determine whether they will be subsidised by the Australian government. This is usually performed from the perspective of the health-care sector rather than from the societal perspective[44]. We will be following these guidelines. In this pilot/feasibility study we will ascertain the feasibility of obtaining the outcome (including QALYs) and cost data in a valid manner, determine how much outcome and cost data are missing, and obtain estimates of mean and standard deviation of outcomes and costs. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[42] statement checklist will also be followed to report the economic evaluation component in the full study.

In this pilot/feasibility study all participants in all study arms have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. *Arm 4, the control arm, therefore is the usual care arm.* In this pilot/feasibility study the perspective of the health sector is undertaken using intention-to-treat. The incremental cost per point on the ODI or QALY (based on EQ5D-L) will be estimated as the ratio of the difference in average cost and ODI or QALY between intervention arms for three comparisons: (i) epidural steroid vs. control, (ii) oral steroid vs. control, and (iii) epidural steroid vs. oral steroid. Missing data will be imputed with iterative Markov chain Monte Carlo methods. Sensitivity analyses will be performed by converting the SF-36 to SF-6D QALYs to compare QALYs, as well as other sensitivity analyses as recommended by CHEERS.

Patient and Public Involvement

Patients and or public were not formally involved in the development of the research question and outcome measures. Patients were not involved in the design of this feasibility study. Patients were not involved in the recruitment to and conduct of this feasibility study. At the end of the study a report of the study results will be provided to all study participants. In this feasibility study of a randomised controlled trial the burden of the intervention was not assessed by patients or the public.

However, the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/15/331/POHW/586), which includes members of the public, assisted with the design and

content of the Patient Information and Consent Form that was developed for this study. As a result of the committee's contribution, the revised Patient Information and Consent Form clearly provides the reason for undertaking the study, the outcome measures involved, explains the nature of the interventions and their burden, and clearly summarises overall study conduct.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by South Eastern Sydney Local Health District Human Research Ethics Committee and is guided by a Data Safety and Monitoring Board and South Eastern Sydney Local Health District Human Research Ethics Executive (HREC15/331) Protocol version 3, 67 April 2016. Any changes to the protocol are reported to this committee.

Data monitoring

A data safety and monitoring committee (DSMC) will meet after the first 10 participants have been randomised to evaluate study conduct and safety. The DSMC will consist of the principal investigator (non-voting), a interventional radiologist, neurosurgeon, rheumatologist, and general physician. Adverse event monitoring and withdrawal of participants are discussed. The DSMC will meet every 4 months. The DSMC will be provided blinded data but unblinded data can be provided for a specific participant if requested by the committee. If requested it will be provided by an investigator who holds the randomisation schedule.

Harms

CT fluoroscopy guided transforaminal lumbar epidural steroid (1 ml) and local anaesthetic (1ml) is used in the management of sciatica of all durations. The risks associated with this procedure include:

Dural puncture: the needle penetrates into the sac encasing the nerves within the spinal canal, causing leakage of fluid contained within the sac, known as CSF (cerebrospinal fluid). The risk of this procedure is approximately 1% and is treated with flat bed rest for four hours.

Infection: most of these are minor (1-2%), however can be serious (<0.1%) requiring hospital admission, intravenous antibiotics and surgery.

Bleeding: this is rare although more common in patients with bleeding disorders and on "blood thinning" medication. Patients who cannot cease their medications will be excluded from the study (e.g. patients with mechanical heart valve, recent deep venous thrombosis and pulmonary embolus, recent cardiac stent). Otherwise, patients on warfarin have an INR and depending on the value will be asked to cease the warfarin 5 days prior to the procedure and an INR will be checked the day before the procedure and the value must be <1.5. Pradaxa (dabigatran) must be ceased 3 days prior to the procedure, aspirin and platelet inhibitors (plavix, iscover, ticlopidine, persantin) ceased 7 days prior to the procedure, clexane cease 24 hours prior to the procedure. NSAIDs and COX2 inhibitors do not need to be ceased.

Nerve damage: from direct needle trauma, or as a consequence of the above mentioned complications is rare.

Stroke and spinal cord injury: Most of the reported serious complications result from inadvertently injecting steroids with particulate matter into blood vessels close to the injection site, which can lead to brain or spinal cord injury. The risk of stroke or spinal cord damage from a transforaminal epidural steroid injection in the back is quite low when done under CT fluoroscopy.

The risks of high dose short term oral corticosteroids are more common (10-20%) and include insomnia, nervousness, increased appetite, indigestion, headache. There are risks in patients with active peptic ulcer disease of perforation, worsening hypertension in patients with severe hypertension, and hyperglycemia in patients with poorly controlled diabetes or on insulin treatment. These patients are excluded from the trial. Patients who are on diet or oral hypoglycemic

medications will be monitored with blood tests to minimise risk of significant hyperglycemia. However, these symptoms and abnormal blood tests will cease with stopping of treatment. There is no risk of suddenly stopping dexamethasone in this study as it is only being administered for 2 weeks.

It is important that women participating in this study are not pregnant or lactating as the study CT scan fluoroscopy radiation, although small, is not zero, and dexamethasone is secreted in breast milk.

An adverse event is any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable or unintended sign, symptom or condition and/or an observation that may or may not be related to the study treatment. A serious adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital/birth defect, condition requiring unnecessary medical or surgical intervention. Solicited reporting of adverse events occurs Days 1 to 7, Weeks 3, 6, 12, 24, 48. Participants can also contact study investigators at any time if they have any concerns. All adverse events are reported to the principal investigator and all serious adverse events are reported to the DMSC and Human Research Ethics Committee.

Auditing
A study meeting to audit trial conduct occurs fortnightly. There is no independent trial audit other than that provided by the DSMC and that required by the Human Research Ethics Committee.

Access to Data and Dissemination
The investigators have access to the final trial dataset. There are no contractual agreements limiting access. Study results of this trial will be submitted for publication in a peer-reviewed journal. Individual level data will be made available after the findings of the study have been published. This data can be used for IPD meta-analyses or for further exploratory research. To obtain this data please contact Marissa Lassere.
The trial is registered on ClinicalTrials. Gov - NCT03240783

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COMPETING INTERESTS STATEMENT
There are no competing interests.

AUTHORS' CONTRIBUTION
Marissa Lassere conceived and designed the study. Marissa Lassere and Kent Johnson wrote the first draft of the protocol. Peter Smerdely, Grant Pickard and Jeanette Thom critically reviewed the protocol for important intellectual content and approved the final version.

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The sponsor had no role in the study design of this protocol and will have no role in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, or authority over any of these activities.

FIGURE LEGEND

Figure 1. Study Flow Chart

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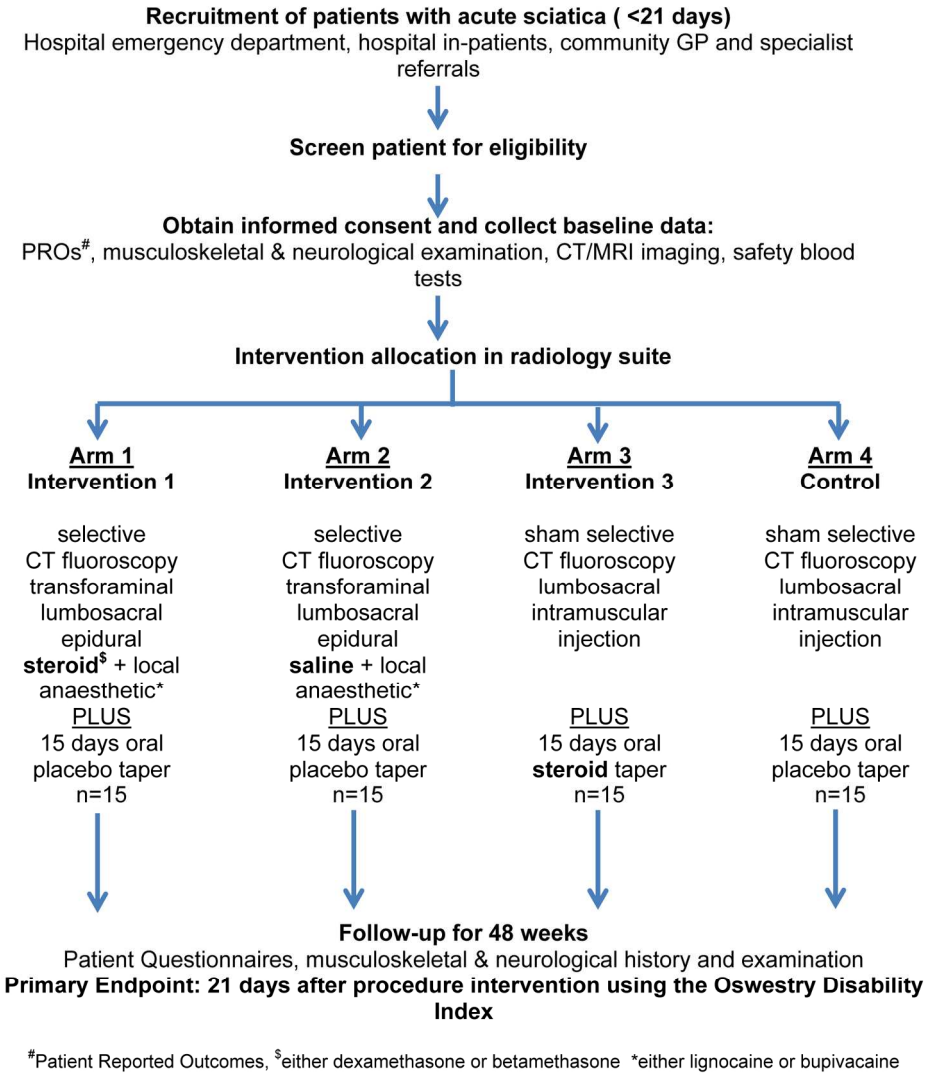

Figure 1. Study Flow Chart

171x184mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4, 7-8
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12,13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17,18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10,11,15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In HREC protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	approved
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	IN HREC protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In patient consent/HREC documentation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	None used
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	HREC
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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