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TITLE

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ABSTRACT

Introduction

Sciatica can be very painful and in most cases is due to pressure on a spinal nerve root from a disc herniation with associated inflammation. For some patients the pain persists and one management option is a spinal epidural steroid injection (ESI). The aim of an ESI is to relieve leg pain, improve function and reduce the need for surgery. ESIs work well in some patients, but not in others but we are unable to identify these patient subgroups currently. The aims of this study are to identify factors, including patient characteristics, clinical examination and imaging findings that help to predict who does well and who doesn't after an ESI. The overall objective is to develop a prognostic model to support individualised patient and clinical decision-making regarding ESI.

Methods

POiSE is a prospective cohort study of 439 patients with sciatica referred by their clinician for an ESI. Participants will receive weekly text messages until 12 weeks following their ESI and then again at 24- weeks following their ESI, to collect leg pain severity data. Questionnaires will be sent to participants at baseline, and at 6, 12 and 24-weeks after their ESI, to collect data on pain, disability, recovery and additional interventions. Prognosis for the cohort will be described. The primary outcome measure for the prognostic model is leg pain at 6 weeks. Prognostic models will also be developed for the secondary outcomes of disability and recovery at 6 weeks and additional interventions at 24 weeks following ESI. Statistical analyses will include multivariable linear and logistic regression with mixed effects model.

Ethics and Dissemination

The POiSE study has received ethical approval (South Central Berkshire B Research Ethics Committee 21/SC/0257). Dissemination will be guided by our patient and public engagement group and will include scientific publications, conference presentations and social media.

Strengths and limitations of this study

1. This large prospective cohort study will deliver new knowledge about the prognosis of patients with sciatica who are eligible for an ESI
2. The study will provide better evidence about factors that can be routinely collected in clinical practice, to predict outcome of patients who have ESI
3. This will support future evidence based decision-making for patients and clinicians considering ESIs as an intervention
4. Patient recruitment will be challenging to achieve the target sample size given the current demands on clinicians' time to identify eligible patients and public health service waiting lists for interventions. This may lead to selection bias.
5. The chosen predictors of outcome are based on data that can be collected in routine clinical care and do not include more costly measurements such as biomarkers

INTRODUCTION

Sciatica is a common variation of low back pain (LBP), usually presenting as sharp, shooting pain in the leg, often with numbness and muscle weakness (1). In most cases sciatica is caused by a lumbar disc herniation compressing the lumbar spinal nerve root(s), with associated inflammation (2). Many patients improve but around 30% continue to suffer from pain and related disability after one year (3, 4). Sciatica is a costly health problem. A Dutch study estimated sciatica-related societal costs to account for 13% of all LBP-related costs (5), this translates to £268 million per year in the UK (6).

Guidelines recommend epidural steroid injections (ESIs) for treating severe disc-related sciatica pain based on trial data that shows modest benefits in terms of leg pain reduction and avoidance of surgery (7-10). ESIs can be performed in a number of ways (caudal, interlaminar and transforaminal approaches), and with or without imaging to verify delivery of the injectate substance to the target level in the spine (8). The term epidural steroid injection (ESI) is used throughout this paper to describe any type of spinal injection (including local anaesthetic and corticosteroid), used for disc-related sciatica for reducing leg pain.

There appears to be wide variation in response to ESIs, with some patients improving to such a degree that spinal surgery is avoided whilst others do not improve (7, 11-14). Little is known about which factors predict outcome from ESIs; patient characteristics, clinical assessment findings, imaging findings or other test results. Anecdotally, we know clinicians use the "flip of a coin" analogy, i.e., explaining to patients that they have a "50:50" chance of improvement from an ESI. A recent randomised controlled trial compared surgical microdiscectomy with TFESI (transforaminal ESI) in patients with disc related sciatica pain with symptom duration of up to 12 months (15). No significant difference was found for pain or disability outcomes and the trial team recommended that TFESI should be considered as a first invasive treatment option. With the need to reduce low value healthcare (16) it would be helpful to be able to better identify patients who have a reasonable chance of benefiting from ESI. This would prevent unnecessary burden on healthcare services and unnecessary healthcare costs because patients who do not improve with ESI may undergo repeat injections or experience delays in proceeding to surgery.

Our recent systematic review investigated factors that might predict outcomes following ESI in patients with disc-related sciatica that can be routinely collected in clinical practice (17). Of 15 eligible studies exploring 42 factors, we found no consistent prognostic factor; most studies found no association between the selected factors and patient outcomes or conflicting results. Overall study quality was low with all judged to have moderate or high risk of bias. There is a clear need for a suitably powered, low risk of bias, prospective cohort to more carefully investigate factors that predict outcome following ESI.

The overall POiSE research question is**:** In adults with disc-related sciatica, can we accurately predict pain and functional outcomes following ESI using patient, clinical and imaging characteristics? The overall aim is to offer patients with disc-related sciatica better information about their likelihood of improvement in leg pain following ESI. Finally, the overall objective is to develop a prognostic model to support individualised patient and clinical decision-making regarding ESI.

The objectives of the POiSE study are:

Objective 1: Describe the characteristics and overall prognosis in patients with sciatica who are referred for ESI for disc related sciatica for (i) the entire cohort (ii) those who have an ESI (iii) those who do not have the ESI

Objective 2: Identify which variables are independent prognostic factors for leg pain at 6 weeks, 12 and 24 weeks following ESI

Objective 3: Develop and internally validate prognostic models to predict leg pain of sciatica patients at 6 weeks following an ESI

Objective 4: Develop and internally validate prognostic models to predict (i) physical function at 6 weeks following ESI, (ii) recovery at 6 weeks following an ESI, and (iii) surgery or further ESI at 24 weeks following ESI

Objective 5: Identify clusters of patients with distinct leg pain trajectories (patterns of changes in pain over time) using weekly leg pain measures until 12 weeks following ESI and 6 months following ESI

Objective 6: Explore if prognostic factor effects differ in those who have an ESI and those who do not

METHODS AND ANALYSIS

The POiSE study is a multi-centre, prospective observational clinical cohort study.

The study will be performed and reported according to the STROBE guidance for strengthening the reporting of observational studies in epidemiology (18). The PROGRESS framework for prognosis research will guide the design and analysis of the cohort study (19, 20) and the TRIPOD statement for transparent reporting of a multivariable prediction model for individual prognosis (21).

Cohort Study setting

This prospective cohort study will be conducted in the National Health Service (NHS) spinal services and will not interfere with or change patients' usual care. Most of these services are called spinal services (some are called interface services), where patients are assessed by specialist clinicians, further imaging (MRI scans) is arranged if needed and onward management is planned.

Spinal services will be identified by the research team, through their clinical and research networks and data from the GIRFT (Getting It Right First Time) report (22) of spinal services will be used to target sites with the highest number of ESI cases performed monthly. Sites will be approached to gauge their interest in becoming a participating site. A minimum number of 10 sites is anticipated to be involved in the study.

Study population

The study population are adults consulting in spinal services with disc-related sciatica. Patients are considered eligible for the study if their clinician considers them appropriate for a referral for an ESI for their sciatica (leg pain) symptoms as part of their routine clinical care and local sciatica management pathways.

Inclusion and Exclusion criteria

Patients that meet the following criteria are eligible to take part:

- Age 18 years and over
- Clinical diagnosis of disc-related sciatica, with concordant MRI findings
- Patient considered by assessing clinician as eligible for a therapeutic ESI as a treatment option

- Patient has access to a mobile phone and is willing to receive/ send text messages for data collection

Patients that meet the following exclusion criteria are unable to take part:

- Patients who are being offered an ESI for diagnostic purposes only
- Patient with symptoms of neurogenic claudication due to spinal stenosis
- Patient unable to provide full informed consent
- Patient unable to read/write English as they would be unable to complete data collection
- Currently pregnant as ESI not routinely offered during pregnancy

Identification of patients for the cohort study

The staff trained in the study procedures will inform potentially eligible patients about the study and ask the patient to consent to have their contact details sent to the research study team so they can receive further information about the study. Patient details will be recorded on an online Consent to Contact (CtoC) survey sent directly to the research study team who will distribute the study pack, via email or by post depending on the patient's preference. Identification of patients can be done at routine clinical appointments with patients when they are referred for the ESI, or from screening waiting lists of patients listed for an ESI in sites with waiting lists for injections. If the patient is not interested in the study, their year of birth and sex will be completed in the online form to record basic demographics of all invited patients. If the patient returns the completed consent form and baseline questionnaire to the research team, they become a participant in the study.

Data Collection

Data collection will be from questionnaires (questionnaire schedule outlined in table 2), case report forms (CRF), text messages, magnetic resonance imaging (MRI) scans and hospital records.

Primary outcome measure

The primary outcome measure for the prognostic model is leg pain intensity (Numerical Rating Scale (NRS) of 0-10). The primary time-point is 6 weeks following the ESI. The leg pain intensity measure will be collected via weekly text message and follow-up questionnaires using the question "In the last week, on average, how intense was your usual sciatica leg pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"? (23).

Secondary outcome measures

The secondary outcome measures for describing overall prognosis and developing prognostic models are

(i) leg pain intensity (NRS 0-10)

(ii) Physical function limitations (Oswestry Disability Index (ODI) 0-100) (24) collected via online and postal questionnaires

(iii) Patient-reported recovery collected via online and postal questionnaires using a 6-point ordinal scale from "completely recovered" to "much worse", where symptoms resolution is defined as a response of either "completely recovered", "much better" or "better" (25)

(iv) Undergone, or listed for surgery for sciatica, or further ESI. These data will be captured in patient completed questionnaires or hospital notes review at 24 weeks following ESI

Baseline descriptive variables

The following descriptive variables will be collected at baseline and are detailed in table 1:

Age at time of baseline questionnaire completion, sex of participant, current smoking status, height and weight to calculate BMI using the formula mass (kg)/height (m^2). BMI categories will be defined according to BMI score ranges as: normal/underweight (<25), overweight (25 to <30) or obese/morbidly obese (30 to > 40). Socio-economic status will be determined based on the participant's current or most recent paid job. The Standard Occupational Classification system will be used to classify job titles into four levels: Managerial and professional occupations (higher); Intermediate occupations (intermediate); Routine and manual occupations (routine); Never worked and long-term unemployed (26).

Back pain intensity (NRS 0-10) will be asked in the same manner as the leg pain intensity question: In the last week, on average, how intense was your usual back pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'. Duration of symptoms (months) will be established from the question. "How long have you had this current bout/episode of sciatica leg pain"? With 13 tick options ranging from "1 month" up to "more than 12 months".

Work related variables will be included for the proportion of employed patients with time off work due to sciatica. Two questions will be asked: "have you self-certified time off work because of your current bout/episode of sciatica leg pain" and "have you been given any "sick notes" or "fit notes" from your doctor because of your current bout/episode of sciatica leg pain? Time off work in the last month (days) due to sciatica will be asked. Interference of pain with work performance will be measured on a 0 to 10 scale where 0 is "not at all" and 10 is "the pain is so bad I am unable to do my job".

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS), scored from 0 (no anxiety or depression) to 21 (high level of anxiety or depression) (27). Comorbidities will be recorded from a list of five conditions (chest problems, heart problems, hypertension, diabetes, circulation problems in legs). Sleep disturbance due to sciatica symptoms will be asked (Jenkins sleep questionnaire) (28). General health will be measured asking patients to rate their health as either good/very good/excellent fair or poor.

Self-reported resource use in the last six to 12 weeks related to their sciatica will be obtained on primary care consultations (general practitioners, practice nurses, other primary care practitioner), secondary care consultations (e.g. Emergency Department, hospital consultants, physiotherapists), private care consultations (e.g. physiotherapists, chiropractors, osteopaths, consultants) prescriptions, hospital based procedures (diagnostic tests, injections, and investigations) and surgery. Medications for sciatica symptoms will be recorded, including analgesics, NSAIDs, opiates, gabapentin, pregabalin, amitriptyline (29, 30). The EQ5D-5L will capture health related quality of life (31).

Predictor variables

The potential predictor variables (Table 1) have been chosen based on the results of an expert consensus study using Delphi methodology (Stynes et al 2023, in preparation). They will be measured by (i) questions in the baseline questionnaire, (ii) items from history and physical clinical

assessment collected in the CRF completed by the clinician before the ESI, and (iii) MRI imaging findings reported before the ESI.

Table 1 Predictor variables collected at baseline

Condition specific factors	Response to treatment for previous episodes Previous history of lumbar spine surgery Duration of current sciatica symptoms Treatment expectations
Work items	Litigation (ongoing claim/secondary gain), Off work due to sciatica symptoms
Medication	Long term opioid medication use (i.e. for >3 months)
Physical function	Physical function measure
Psychological	Pain catastrophising Self-efficacy Anxiety Depression Distress and somatisation Fear avoidance beliefs
Pain	Leg pain greater than back pain Presence of neuropathic pain features Sleep disturbed due to sciatica symptoms Number of additional pain sites in the body Constant or intermittent leg pain Bilateral leg symptoms.
Clinical assessment	Positive Straight Leg Raise (SLR) test Leg pain distribution
MRI findings	Grade of nerve root compression Associated spinal stenosis/degenerative changes (at the segment affected by the herniation) Type of disc herniation
Injection items	Type of injection (e.g. transforaminal ESI, caudal ESI)

Follow-up variables

In addition to the secondary outcomes for the prognostic models, the following variables will be collected in the 6-week, 12-week and 24-week questionnaires (12 weeks, 18 weeks and 30 weeks for participants that decline ESI referral) to describe the clinical course of the cohort; NRS scores for back and leg pain, sleep disturbance, anxiety and depression, days lost from work in the last month due to sciatica, pain medication and additional healthcare use.

Table 2 POiSE data collection from questionnaire schedule

Description	**Measure**	**Baseline**	**6 weeks***	**12 weeks***	**24 weeks***
Primary Outcome measure					

Leg pain intensity	In the last week, on average, how intense was your usual sciatica leg pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"	✓	✓	✓	✓
Secondary Outcome measures					
Recovery	Single item question		✓	✓	✓
Physical Function	Oswestry Disability index 10 items scored 0 to 5 and can be converted to a percentage. Higher scores indicate higher disability level	✓	✓	✓	✓
Proceed to surgery or second injection	Two single item questions	✗	✓	✓	✓
Sociodemographics					
Age	Date of birth	✓			
Sex at birth	Male / Female	✓			
Smoking status	Two single item questions	✓			
Socio-economic status	Current or most recent paid job	✓			
Sciatica pain characteristics					
Duration of sciatica symptoms	How long (months) have you had this current bout /episode of sciatica leg pain?	✓			
History of previous episodes	Single item question	✓			
Constant or intermittent pain	Single item question	✓			
Back pain intensity	In the last week, on average, how intense was your usual back pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"	✓	✓	✓	✓
Sleep	Jenkins sleep questionnaire	✓	✓	✓	✓
Presence of Neuropathic pain features	Two single item questions	✓			
Leg pain distribution	Full body manikin	✓			
Number of additional pain sites	Full body manikin	✓			
Comorbidities and lifestyle					
Height and weight (BMI)	Self-reported	✓			
Comorbidities	Self-reported, pre-defined list	✓			
General health	Single item question	✓			
Health related quality of life	EQ5D-5L	✓	✓	✓	✓
Analgesic use	Over the counter and prescribed	✓	✓	✓	✓
Work related factors					
Current work situation	Single item question	✓	✓	✓	✓
Time off work	Two single item questions	✓	✓	✓	✓
Work absence	Number of days off work in the past month (days)	✓	✓	✓	✓
Work performance	0-10 NRS scale where 0=not at all affected, 10=pain is so bad that unable to do job.	✓	✓	✓	✓
Litigation	Single item question	✓			
Psychosocial and behavioural factors					
Anxiety and Depression	Hospital Anxiety and Depression Scale (HADS) scored from 0 (no anxiety and depression) to 21	✓	✓	✓	✓

	(high levels of anxiety and depression)				
Self Efficacy	How confident have you felt this week about managing your sciatica pain? (0=not at all, 10= extremely confident)	✓			
Fear of movement	Two single item questions	✓			
Pain Catastrophising	Single item question	✓			
Treatment expectations	How confident are you that the treatment you are receiving will help your sciatica leg pain? 0=not at all confident, 10= extremely confident)	✓			
Distress	Over the last 2 weeks, on average, how much distress have you been experiencing because of your sciatica leg pain? 0-10 no distress-extreme distress.	✓			
Healthcare use					
Additional healthcare use	Self-report: consultations with Health care professionals, prescriptions and procedures (further ESI and surgery)	✓	✓	✓	✓
*Questionnaire data collection schedule for patients who decline ESI will be 12 weeks, 18 weeks and 30 weeks after baseline					

Text message data

Text messages will be initiated once the patient consents to take part in the cohort study. Weekly text messages asking about leg pain intensity will continue every 7 days after their first text until 12 weeks after the scheduled ESI and a final text message will be sent at 24 weeks after the ESI. The weekly text message will also ask the participant to contact the study team with the date of their scheduled ESI if known, this message will stop after the scheduled date of the ESI. Participants who do not respond to their text message will receive a reminder message 48 hours later.

MRI scan findings

A consultant radiologist will report the MRI scans of all participants in a standardised approach. The report will only include the MRI potential predictors agreed following the consensus study. The data recorded will include the type of disc herniation (e.g. protrusion, extrusion), and associated spinal stenosis/degenerative changes at the segment affected by the herniation and the grade (severity) of nerve root compression. Arrangements will be made with participating sites to transfer the anonymised MRI images to the site handling the MRI images either electronically or post images on a compact disc. The images will be pseudo-anonymised to only include the participant study ID number so their POiSE scan report can be linked with the questionnaire, CRF and pain data.

ANALYSIS

Sample size/Power calculation

The target sample size for the ESI prognostic model is 351 participants with data for the primary outcome (leg pain intensity) at 6 weeks. As some participants may withdraw or be lost to follow-up, we will aim to recruit 439 participants to ensure 351 with data for the primary outcome. The sample size ensures precise parameter estimates and also reduces the potential for overfitting in model

development, based on the criteria by Riley et al.(32). This suggests a minimum of 351 participants are needed to allow us to examine up to 25 prognostic factor parameters (and thus 14 participants per parameter) for model inclusion, ensures a precise estimate of the model intercept and (assuming the model R^2 of at least 30%) small overfitting (e.g. small difference of < 0.05 in the apparent and adjusted R^2, and target shrinkage factor of about 0.9) (33).

In terms of prognostic factor effect sizes, when considering a binary factor with a 10% prevalence in one of the two categories, 191 participants are required to detect an unadjusted mean difference in pain score of 1.0 point between groups (those reporting they are improved versus not improved after ESI) with 80% power and a 5% two-tailed significance level, assuming a standard deviation of 1.5 points for pain intensity scores (34). The intended sample size is more than 150 greater than the required 191, which will allow adjustment for multiple testing and correlation amongst factors via a variance inflation factor (35).

Overall prognosis (objective 1)

We intend to summarise the overall prognosis of the entire cohort as well as those groups of participants who receive an ESI and those that do not (although we expect the latter to be a smaller group of participants). Leg pain intensity, disability and recovery will be summarised at the different follow-up time-points to represent short, medium and long term prognoses. Frequencies and percentages of missing outcomes will be summarised for each time-point. The main analysis will summarise available outcome data for the time-points of interest (ignoring missing values). If the proportion of missing values is large, then a sensitivity analysis will be conducted using multiple imputation in which missing outcomes will be imputed using outcome values from the other time-points. The frequency of missing responses will be considered e.g. a single missing response for a participant who otherwise responded regularly, versus no responses for a participant beyond a certain time-point which may signify the individual withdrawing from the study without contacting the research team to inform them of their withdrawal from the research.

Prognostic factors (primary objective 2)

To determine prognostic factors associated with the primary outcome (leg pain intensity) at the three time-points (6, 12 and 24-weeks), multivariable linear regression will be used to investigate the associations between potential prognostic factors and leg pain in the ESI group. The independent prognostic value of each factor will be evaluated after accounting for all other potential prognostic factors by including them all in the multivariable model. In addition, the variables “type of injection” (e.g. caudal or transforaminal epidural) and “duration of symptoms up to time of injection” will be included in the model as well as “baseline leg pain intensity score”. Non-linear associations will be explored for continuous factors using multivariable fractional polynomials (thus avoiding categorisation).

Prognostic models for primary outcome (primary objective 3)

A pre-defined set of prognostic factors (corresponding to up to 25 parameters) will be considered for inclusion in a multivariable linear regression model to predict leg pain intensity outcome at 6 weeks following ESI. The model will be developed using backward elimination and a p-value for exclusion of 0.157 (corresponding to selection based on Akaike’s Information Criteria) (36). Factors that reached consensus as to their potential role in predicting outcome following ESI from the Delphi study will be retained in the model regardless of statistical significance, including baseline leg pain intensity. For comparison, a full model (with all variables included) will also be estimated (33). Fractional polynomials will be considered for modelling non-linear continuous variables using multivariable fractional polynomial modelling (37) This procedure performs a series of tests for each continuous variable to compare more complex non-linear functions (using a second degree fractional

polynomial function FP2) to simpler non-linear functions (using a first degree fractional polynomial function, FP1) and a linear function.

Internal validation

Apparent model performance will be quantified using the R^2 statistic and calibration plots (and associated measures such as calibration slope and calibration-in-the-large) estimated in the model development dataset (33). Optimism due to potential overfitting will then be checked and adjusted for using an internal validation approach via bootstrapping.. We will obtain 1000 bootstrap samples (each the same size as the original dataset) by sampling (with replacement) individuals from the original dataset. Then, to examine potential overfitting and produce optimism-adjusted performance estimates, in each bootstrap sample, a new model will be produced using the same process (e.g. backwards selection) as above, and the model's predictive performance then evaluated on the original sample. The average difference in the bootstrap models' apparent performance (in the bootstrap sample) and the test performance (in the original dataset) provide the optimism for each performance measures. Optimism-adjusted estimates of performance will then be derived by subtracting the optimism estimates from the original apparent performance estimates for the original model. Finally, shrinkage will be applied to correct for overfitting by multiplying the original model's beta regression coefficients (predictor effects in the original model) by a uniform shrinkage factor (equal to the optimism-adjusted calibration slope) and by then re-estimating the intercept to ensure overall calibration-in-the-large whilst constraining the revised predictor effects at their shrunken value. (33). This will give the final model.

Regression coefficients along with standard errors and 95% confidence intervals will be reported for the original (pre-shrinkage) model. Regression coefficients alone will be reported for the final shrunken model. Performance measures will be reported with 95% confidence intervals for the apparent performance as well as estimates of optimism-corrected performance from the internal validation.

For comparison, a full model forcing in all candidate prognostic factors will be produced avoiding backwards selection, with otherwise the same process of model development and internal validation as described above. Also, a model developed using a multivariate linear regression accounting for the correlation of outcome values at 6, 12 and 24 weeks will be considered.

Prognostic models for secondary outcomes (objective 4)

Model development for physical function at 6 weeks will follow the same strategy as for the primary outcome of leg pain intensity described above. For recovery at 6 weeks and surgery or further ESI at 24 weeks, which are both binary outcomes, logistic regression models will be used instead of linear regression models. For these two logistic models, discrimination will be assessed (using the C-statistic) in addition to calculating measures of calibration, and clinical utility assessed using net benefit and decision curves, with the range of important risk thresholds pre-defined based on consultation with clinicians and patients.

Missing data

Missing data will be summarised as frequencies and proportions for each variable. Multiple imputation will be used to handle missing data, using multivariate imputation by chained equations and assuming data are missing at random. Reasons for the missing values will be explored to investigate whether the missing at random assumption is reasonable. The number of imputations will be selected to correspond to the proportion of individuals with any missing data (38) and all variables considered for inclusion in the prognostic model will be included in the imputation model,

as well as including the outcome variables. Rubin's rules will be used to combine estimates across imputations (39).

Leg pain trajectories (objective 5)

Latent class growth analysis (40, 41) will be used to identify distinct groups (clusters) of participants with similar trajectories of leg pain intensity using weekly leg pain data form text message responses. Analysis will use those with baseline plus at least two follow-up measures within the three-month timeframe. Appropriate polynomial functional form for each trajectory will be chosen and statistical indices used to assess model fit will include the Bayesian Information Criterion and bootstrapped likelihood ratio test. Participants will be assigned to trajectories according to maximum probability assignment principle (42). Baseline patient characteristics associated with membership of each trajectory and treatment will be described.

Outcomes and prognostic factors in ESI and non-ESI subgroups (objective 6)

Some individuals decline a referral for an ESI, are referred but recover while on the waiting list, or choose to have other treatments such as surgery. To explore whether the effects of some prognostic factors differ in individuals who have an ESI and those that do not, we will use the combined dataset of both ESI and non-ESI patients, if there are sufficient participants recruited in the non-ESI pathway. A cohort of approximately 90 non-ESI participants will be large enough to explore the interaction between factors identified in the final ESI prognostic model and treatment outcomes.

A linear regression model for 6-week leg pain intensity will be fitted that includes the linear combination of predictor effects from the model derived for objective 3 as a predictor, treatment (ESI vs no-ESI) and an interaction term between the linear predictor and treatment. If this interaction is significant, further exploration of interactions between individual predictors and treatment will be undertaken. If the interaction is not significant, this would suggest they are generic predictive factors and not to do with treatment (i.e. treatment moderators). This will be exploratory analysis as the sample size is not powered for this analysis.

Ethics and Dissemination

The POiSE study has received ethical approval (South Central Berkshire B Research Ethics Committee 21/SC/0257). We have adopted the approach advocated by INVOLVE Standards for Patient and Public involvement (PPIE). PPIE input will be key to sharing results and brainstorming dissemination and future implementation ideas and strategies. A consensus workshop is planned with patients and clinicians to discuss the research findings and how they might progress to develop into a clinical tool. Findings of the POiSE study will be presented at national and international conferences and published in peer reviewed journals. Once the results of the study have been published, further dissemination will be shared with the wider public. Members of the POiSE PPIE group will help interpret the study findings from a patient perspective; advising on how best to publicise the study findings to the wider public and supporting the design of evidence-based information materials (e.g. leaflets, online tools, patient stories) for clinicians and patients to use when considering ESI as a management option for disc-related sciatica.

After publication of the results of the cohort study, depersonalised datasets will be available upon request from primarycare.datasharing@keele.ac.uk.

Study status

Patient recruitment and follow-up is expected to continue until the end of 2024. Recruitment has started with more than 250 patients recruited by June 2023. The study is no longer recruiting additional NHS spinal sites to identify eligible patients.

Registration details

Research Registry www.researchregistry.com: UIN: researchregistry6844

Author Contributions

SS conceived the study. NF, RR, KK, RO and JO'D helped SS shape the fellowship application to secure funding for the POiSE study. SS led the design of the study with the support of her mentorship team NF, KK, RR, KS, RO and JO'D. RR and KS prepared the analysis plan. ND and SS will perform the analysis, supported by KS. AC and SS are responsible for project management and coordination activities of the study and ND is contributing to data monitoring and reporting. SS prepared the draft of the manuscript which all authors critically reviewed and approved the final version.

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Competing interests statement

None declared

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Predictors of outcome in sciatica patients following an epidural steroid injection. The POiSE prospective observational cohort study protocol.

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TITLE

Predictors of outcome in sciatica patients following an epidural steroid injection. The POiSE prospective observational cohort study protocol.

ABSTRACT

Introduction

Sciatica can be very painful and in most cases is due to pressure on a spinal nerve root from a disc herniation with associated inflammation. For some patients the pain persists and one management option is a spinal epidural steroid injection (ESI). The aim of an ESI is to relieve leg pain, improve function and reduce the need for surgery. ESIs work well in some patients, but not in others but we are unable to identify these patient subgroups currently. The aims of this study are to identify factors, including patient characteristics, clinical examination and imaging findings that help to predict who does well and who doesn't after an ESI. The overall objective is to develop a prognostic model to support individualised patient and clinical decision-making regarding ESI.

Methods

POiSE is a prospective cohort study of 439 patients with sciatica referred by their clinician for an ESI. Participants will receive weekly text messages until 12 weeks following their ESI and then again at 24- weeks following their ESI, to collect leg pain severity data. Questionnaires will be sent to participants at baseline, and at 6, 12 and 24-weeks after their ESI, to collect data on pain, disability, recovery and additional interventions. Prognosis for the cohort will be described. The primary outcome measure for the prognostic model is leg pain at 6 weeks. Prognostic models will also be developed for the secondary outcomes of disability and recovery at 6 weeks and additional interventions at 24 weeks following ESI. Statistical analyses will include multivariable linear and logistic regression with mixed effects model.

Ethics and Dissemination

The POiSE study has received ethical approval (South Central Berkshire B Research Ethics Committee 21/SC/0257). Dissemination will be guided by our patient and public engagement group and will include scientific publications, conference presentations and social media.

Strengths and limitations of this study

1. This large prospective cohort study will deliver new knowledge about the prognosis of patients with sciatica who are eligible for an ESI
2. The study will provide better evidence about factors that can be routinely collected in clinical practice, to predict outcome of patients who have ESI
3. This will support future evidence based decision-making for patients and clinicians considering ESIs as an intervention
4. Patient recruitment will be challenging to achieve the target sample size given the current demands on clinicians' time to identify eligible patients and public health service waiting lists for interventions. This may lead to selection bias.
5. The chosen predictors of outcome are based on data that can be collected in routine clinical care and do not include more costly measurements such as biomarkers

INTRODUCTION

Sciatica is a common variation of low back pain (LBP), usually presenting as sharp, shooting pain in the leg, often with numbness and muscle weakness (1). In most cases sciatica is caused by a lumbar disc herniation compressing the lumbar spinal nerve root(s), with associated inflammation (2). Many patients improve but around 30% continue to suffer from pain and related disability after one year (3, 4). Sciatica is a costly health problem. A Dutch study estimated sciatica-related societal costs to account for 13% of all LBP-related costs (5), this translates to £268 million per year in the UK (6).

Guidelines recommend epidural steroid injections (ESIs) for treating severe disc-related sciatica pain based on trial data that shows modest benefits in terms of leg pain reduction and avoidance of surgery (7-10). ESIs can be performed in a number of ways (caudal, interlaminar and transforaminal approaches), and with or without imaging to verify delivery of the injectate substance to the target level in the spine (8). The term epidural steroid injection (ESI) is used throughout this paper to describe any type of spinal injection (including local anaesthetic and corticosteroid), used for disc-related sciatica for reducing leg pain.

There appears to be wide variation in response to ESIs, with some patients improving to such a degree that spinal surgery is avoided whilst others do not improve (7, 11-14). Little is known about which factors predict outcome from ESIs; patient characteristics, clinical assessment findings, imaging findings or other test results. Anecdotally, we know clinicians use the "flip of a coin" analogy, i.e., explaining to patients that they have a "50:50" chance of improvement from an ESI. A recent randomised controlled trial compared surgical microdiscectomy with TFESI (transforaminal ESI) in patients with disc related sciatica pain with symptom duration of up to 12 months (15). No significant difference was found for pain or disability outcomes and the trial team recommended that TFESI should be considered as a first invasive treatment option. With the need to reduce low value healthcare (16) it would be helpful to be able to better identify patients who have a reasonable chance of benefiting from ESI. This would prevent unnecessary burden on healthcare services and unnecessary healthcare costs because patients who do not improve with ESI may undergo repeat injections or experience delays in proceeding to surgery.

Our recent systematic review investigated factors that might predict outcomes following ESI in patients with disc-related sciatica that can be routinely collected in clinical practice (17). Of 15 eligible studies exploring 42 factors, we found no consistent prognostic factor; most studies found no association between the selected factors and patient outcomes or conflicting results. Overall study quality was low with all judged to have moderate or high risk of bias. There is a clear need for a suitably powered, low risk of bias, prospective cohort to more carefully investigate factors that predict outcome following ESI.

The overall POiSE research question is**:** In adults with disc-related sciatica, can we accurately predict pain and functional outcomes following ESI using patient, clinical and imaging characteristics? The overall aim is to offer patients with disc-related sciatica better information about their likelihood of improvement in leg pain following ESI. Finally, the overall objective is to develop a prognostic model to support individualised patient and clinical decision-making regarding ESI.

The objectives of the POiSE study are:

Objective 1: Describe the characteristics and overall prognosis in patients with sciatica who are referred for ESI for disc related sciatica for (i) the entire cohort (ii) those who have an ESI (iii) those who do not have the ESI

Objective 2: Identify which variables are independent prognostic factors for leg pain at 6 weeks, 12 and 24 weeks following ESI

Objective 3: Develop and internally validate prognostic models to predict leg pain of sciatica patients at 6 weeks following an ESI

Objective 4: Develop and internally validate prognostic models to predict (i) physical function at 6 weeks following ESI, (ii) recovery at 6 weeks following an ESI, and (iii) surgery or further ESI at 24 weeks following ESI

Objective 5: Identify clusters of patients with distinct leg pain trajectories (patterns of changes in pain over time) using weekly leg pain measures until 12 weeks following ESI and 6 months following ESI

Objective 6: Explore if prognostic factor effects differ in those who have an ESI and those who do not

METHODS

The POiSE study is a multi-centre, prospective observational clinical cohort study.

The study will be performed and reported according to the STROBE guidance for strengthening the reporting of observational studies in epidemiology (18). The PROGRESS framework for prognosis research will guide the design and analysis of the cohort study (19, 20) and the TRIPOD statement for transparent reporting of a multivariable prediction model for individual prognosis (21).

Cohort Study setting

This prospective cohort study will be conducted in the National Health Service (NHS) spinal services and will not interfere with or change patients' usual care. Most of these services are called spinal services (some are called interface services), where patients are assessed by specialist clinicians, further imaging (MRI scans) is arranged if needed and onward management is planned.

Spinal services will be identified by the research team, through their clinical and research networks and data from the GIRFT (Getting It Right First Time) report (22) of spinal services will be used to target sites with the highest number of ESI cases performed monthly. Sites will be approached to gauge their interest in becoming a participating site. A minimum number of 10 sites is anticipated to be involved in the study.

Study population

The study population are adults consulting in spinal services with disc-related sciatica. Patients are considered eligible for the study if their clinician considers them appropriate for a referral for an ESI for their sciatica (leg pain) symptoms as part of their routine clinical care and local sciatica management pathways.

Inclusion and Exclusion criteria

Patients that meet the following criteria are eligible to take part:

- Age 18 years and over
- Clinical diagnosis of disc-related sciatica, with concordant MRI findings
- Patient considered by assessing clinician as eligible for a therapeutic ESI as a treatment option

- Patient has access to a mobile phone and is willing to receive/ send text messages for data collection

Patients that meet the following exclusion criteria are unable to take part:

- Patients who are being offered an ESI for diagnostic purposes only
- Patient with symptoms of neurogenic claudication due to spinal stenosis
- Patient unable to provide full informed consent
- Patient unable to read/write English as they would be unable to complete data collection
- Currently pregnant as ESI not routinely offered during pregnancy

Identification of patients for the cohort study

The staff trained in the study procedures will inform potentially eligible patients about the study and ask the patient to consent to have their contact details sent to the research study team so they can receive further information about the study. Patient details will be recorded on an online Consent to Contact (CtoC) survey sent directly to the research study team who will distribute the study pack, via email or by post depending on the patient's preference. Identification of patients can be done at routine clinical appointments with patients when they are referred for the ESI, or from screening waiting lists of patients listed for an ESI in sites with waiting lists for injections. If the patient is not interested in the study, their year of birth and sex will be completed in the online form to record basic demographics of all invited patients. If the patient returns the completed consent form and baseline questionnaire to the research team, they become a participant in the study.

Data Collection

Data collection will be from questionnaires, case report forms (CRF), text messages, magnetic resonance imaging (MRI) scans and hospital records.

Primary outcome measure

The primary outcome measure for the prognostic model is leg pain intensity (Numerical Rating Scale (NRS) of 0-10). The primary time-point is 6 weeks following the ESI. The leg pain intensity measure will be collected via weekly text message and follow-up questionnaires using the question "In the last week, on average, how intense was your usual sciatica leg pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"? (23).

Secondary outcome measures

The secondary outcome measures for describing overall prognosis and developing prognostic models are

(i) leg pain intensity (NRS 0-10)

(ii) Physical function limitations (Oswestry Disability Index (ODI) 0-100) (24) collected via online and postal questionnaires

(iii) Patient-reported recovery collected via online and postal questionnaires using a 6-point ordinal scale from "completely recovered" to "much worse", where symptoms resolution is defined as a response of either "completely recovered", "much better" or "better" (25)

(iv) Undergone, or listed for surgery for sciatica, or further ESI. These data will be captured in patient completed questionnaires or hospital notes review at 24 weeks following ESI

Baseline descriptive variables

The following descriptive variables will be collected at baseline and are detailed in table 1:

Age at time of baseline questionnaire completion, sex of participant, current smoking status, height and weight to calculate BMI using the formula mass (kg)/height (m^2). BMI categories will be defined according to BMI score ranges as: normal/underweight (<25), overweight (25 to <30) or obese/morbidly obese (30 to > 40). Socio-economic status will be determined based on the participant's current or most recent paid job. The Standard Occupational Classification system will be used to classify job titles into four levels: Managerial and professional occupations (higher); Intermediate occupations (intermediate); Routine and manual occupations (routine); Never worked and long-term unemployed (26).

Back pain intensity (NRS 0-10) will be asked in the same manner as the leg pain intensity question: In the last week, on average, how intense was your usual back pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'. Duration of symptoms (months) will be established from the question. "How long have you had this current bout/episode of sciatica leg pain"? With 13 tick options ranging from "1 month" up to "more than 12 months".

Work related variables will be included for the proportion of employed patients with time off work due to sciatica. Two questions will be asked: "have you self-certified time off work because of your current bout/episode of sciatica leg pain" and "have you been given any "sick notes" or "fit notes" from your doctor because of your current bout/episode of sciatica leg pain? Time off work in the last month (days) due to sciatica will be asked. Interference of pain with work performance will be measured on a 0 to 10 scale where 0 is "not at all" and 10 is "the pain is so bad I am unable to do my job".

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS), scored from 0 (no anxiety or depression) to 21 (high level of anxiety or depression) (27). Comorbidities will be recorded from a list of five conditions (chest problems, heart problems, hypertension, diabetes, circulation problems in legs). Sleep disturbance due to sciatica symptoms will be asked (Jenkins sleep questionnaire) (28). General health will be measured asking patients to rate their health as either good/very good/excellent fair or poor.

Self-reported resource use in the last six to 12 weeks related to their sciatica will be obtained on primary care consultations (general practitioners, practice nurses, other primary care practitioner), secondary care consultations (e.g. Emergency Department, hospital consultants, physiotherapists), private care consultations (e.g. physiotherapists, chiropractors, osteopaths, consultants) prescriptions, hospital based procedures (diagnostic tests, injections, and investigations) and surgery. Medications for sciatica symptoms will be recorded, including analgesics, NSAIDs, opiates, gabapentin, pregabalin, amitriptyline (29, 30). The EQ5D-5L will capture health related quality of life (31).

Predictor variables

The potential predictor variables (Table 1) have been chosen based on the results of an expert consensus study using Delphi methodology (Stynes et al 2023, in preparation). They will be measured by (i) questions in the baseline questionnaire, (ii) items from history and physical clinical

assessment collected in the CRF completed by the clinician before the ESI, and (iii) MRI imaging findings reported before the ESI.

Table 1 Predictor variables collected at baseline

Condition specific factors	Response to treatment for previous episodes Previous history of lumbar spine surgery Duration of current sciatica symptoms Treatment expectations
Work items	Litigation (ongoing claim/secondary gain), Off work due to sciatica symptoms
Medication	Long term opioid medication use (i.e. for >3 months)
Physical function	Physical function measure
Psychological	Pain catastrophising Self-efficacy Anxiety Depression Distress and somatisation Fear avoidance beliefs
Pain	Leg pain greater than back pain Presence of neuropathic pain features Sleep disturbed due to sciatica symptoms Number of additional pain sites in the body Constant or intermittent leg pain Bilateral leg symptoms.
Clinical assessment	Positive Straight Leg Raise (SLR) test Leg pain distribution
MRI findings	Grade of nerve root compression Associated spinal stenosis/degenerative changes (at the segment affected by the herniation) Type of disc herniation
Injection items	Type of injection (e.g. transforaminal ESI, caudal ESI)

Follow-up variables

In addition to the secondary outcomes for the prognostic models, the following variables will be collected in the 6-week, 12-week and 24-week questionnaires (12 weeks, 18 weeks and 30 weeks for participants that decline ESI referral) to describe the clinical course of the cohort; NRS scores for back and leg pain, sleep disturbance, anxiety and depression, days lost from work in the last month due to sciatica, pain medication and additional healthcare use. See table 2 for data collection from questionnaires.

Table 2 POiSE data collection from questionnaire schedule

Description	**Measure**	**Baseline**	**6 weeks***	**12 weeks***	**24 weeks***
Primary Outcome measure					

Leg pain intensity	In the last week, on average, how intense was your usual sciatica leg pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"	✓	✓	✓	✓
Secondary Outcome measures					
Recovery	Single item question		✓	✓	✓
Physical Function	Oswestry Disability index 10 items scored 0 to 5 and can be converted to a percentage. Higher scores indicate higher disability level	✓	✓	✓	✓
Proceed to surgery or second injection	Two single item questions	✗	✓	✓	✓
Sociodemographics					
Age	Date of birth	✓			
Sex at birth	Male / Female	✓			
Smoking status	Two single item questions	✓			
Socio-economic status	Current or most recent paid job	✓			
Sciatica pain characteristics					
Duration of sciatica symptoms	How long (months) have you had this current bout /episode of sciatica leg pain?	✓			
History of previous episodes	Single item question	✓			
Constant or intermittent pain	Single item question	✓			
Back pain intensity	In the last week, on average, how intense was your usual back pain rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be"	✓	✓	✓	✓
Sleep	Jenkins sleep questionnaire	✓	✓	✓	✓
Presence of Neuropathic pain features	Two single item questions	✓			
Leg pain distribution	Full body manikin	✓			
Number of additional pain sites	Full body manikin	✓			
Comorbidities and lifestyle					
Height and weight (BMI)	Self-reported	✓			
Comorbidities	Self-reported, pre-defined list	✓			
General health	Single item question	✓			
Health related quality of life	EQ5D-5L	✓	✓	✓	✓
Analgesic use	Over the counter and prescribed	✓	✓	✓	✓
Work related factors					
Current work situation	Single item question	✓	✓	✓	✓
Time off work	Two single item questions	✓	✓	✓	✓
Work absence	Number of days off work in the past month (days)	✓	✓	✓	✓
Work performance	0-10 NRS scale where 0=not at all affected, 10=pain is so bad that unable to do job.	✓	✓	✓	✓
Litigation	Single item question	✓			
Psychosocial and behavioural factors					
Anxiety and Depression	Hospital Anxiety and Depression Scale (HADS) scored from 0 (no anxiety and depression) to 21	✓	✓	✓	✓

	(high levels of anxiety and depression)				
Self Efficacy	How confident have you felt this week about managing your sciatica pain? (0=not at all, 10= extremely confident)	✓			
Fear of movement	Two single item questions	✓			
Pain Catastrophising	Single item question	✓			
Treatment expectations	How confident are you that the treatment you are receiving will help your sciatica leg pain? 0=not at all confident, 10= extremely confident)	✓			
Distress	Over the last 2 weeks, on average, how much distress have you been experiencing because of your sciatica leg pain? 0-10 no distress-extreme distress.	✓			
Healthcare use					
Additional healthcare use	Self-report: consultations with Health care professionals, prescriptions and procedures (further ESI and surgery)	✓	✓	✓	✓
*Questionnaire data collection schedule for patients who decline ESI will be 12 weeks, 18 weeks and 30 weeks after baseline					

Text message data

Text messages will be initiated once the patient consents to take part in the cohort study. Weekly text messages asking about leg pain intensity will continue every 7 days after their first text until 12 weeks after the scheduled ESI and a final text message will be sent at 24 weeks after the ESI. The weekly text message will also ask the participant to contact the study team with the date of their scheduled ESI if known, this message will stop after the scheduled date of the ESI. Participants who do not respond to their text message will receive a reminder message 48 hours later.

MRI scan findings

A consultant radiologist will report the MRI scans of all participants in a standardised approach. The report will only include the MRI potential predictors agreed following the consensus study. The data recorded will include the type of disc herniation (e.g. protrusion, extrusion), and associated spinal stenosis/degenerative changes at the segment affected by the herniation and the grade (severity) of nerve root compression. Arrangements will be made with participating sites to transfer the anonymised MRI images to the site handling the MRI images either electronically or post images on a compact disc. The images will be pseudo-anonymised to only include the participant study ID number so their POiSE scan report can be linked with the questionnaire, CRF and pain data.

Data analysis plan

Sample size/Power calculation

The target sample size for the ESI prognostic model is 351 participants with data for the primary outcome (leg pain intensity) at 6 weeks. As some participants may withdraw or be lost to follow-up, we will aim to recruit 439 participants to ensure 351 with data for the primary outcome. The sample size ensures precise parameter estimates and also reduces the potential for overfitting in model

development, based on the criteria by Riley et al.(32). This suggests a minimum of 351 participants are needed to allow us to examine up to 25 prognostic factor parameters (and thus 14 participants per parameter) for model inclusion, ensures a precise estimate of the model intercept and (assuming the model R^2 of at least 30%) small overfitting (e.g. small difference of < 0.05 in the apparent and adjusted R^2, and target shrinkage factor of about 0.9) (33).

In terms of prognostic factor effect sizes, when considering a binary factor with a 10% prevalence in one of the two categories, 191 participants are required to detect an unadjusted mean difference in pain score of 1.0 point between groups (those reporting they are improved versus not improved after ESI) with 80% power and a 5% two-tailed significance level, assuming a standard deviation of 1.5 points for pain intensity scores (34). The intended sample size is more than 150 greater than the required 191, which will allow adjustment for multiple testing and correlation amongst factors via a variance inflation factor (35).

Overall prognosis (objective 1)

We intend to summarise the overall prognosis of the entire cohort as well as those groups of participants who receive an ESI and those that do not (although we expect the latter to be a smaller group of participants). Leg pain intensity, disability and recovery will be summarised at the different follow-up time-points to represent short, medium and long term prognoses. Frequencies and percentages of missing outcomes will be summarised for each time-point. The main analysis will summarise available outcome data for the time-points of interest (ignoring missing values). If the proportion of missing values is large, then a sensitivity analysis will be conducted using multiple imputation in which missing outcomes will be imputed using outcome values from the other time-points. The frequency of missing responses will be considered e.g. a single missing response for a participant who otherwise responded regularly, versus no responses for a participant beyond a certain time-point which may signify the individual withdrawing from the study without contacting the research team to inform them of their withdrawal from the research.

Prognostic factors (primary objective 2)

To determine prognostic factors associated with the primary outcome (leg pain intensity) at the three time-points (6, 12 and 24-weeks), multivariable linear regression will be used to investigate the associations between potential prognostic factors and leg pain in the ESI group. The independent prognostic value of each factor will be evaluated after accounting for all other potential prognostic factors by including them all in the multivariable model. In addition, the variables “type of injection” (e.g. caudal or transforaminal epidural) and “duration of symptoms up to time of injection” will be included in the model as well as “baseline leg pain intensity score”. Non-linear associations will be explored for continuous factors using multivariable fractional polynomials (thus avoiding categorisation).

Prognostic models for primary outcome (primary objective 3)

A pre-defined set of prognostic factors (corresponding to up to 25 parameters) will be considered for inclusion in a multivariable linear regression model to predict leg pain intensity outcome at 6 weeks following ESI. The model will be developed using backward elimination and a p-value for exclusion of 0.157 (corresponding to selection based on Akaike’s Information Criteria) (36). Factors that reached consensus as to their potential role in predicting outcome following ESI from the Delphi study will be retained in the model regardless of statistical significance, including baseline leg pain intensity. For comparison, a full model (with all variables included) will also be estimated (33). Fractional polynomials will be considered for modelling non-linear continuous variables using multivariable fractional polynomial modelling (37) This procedure performs a series of tests for each continuous variable to compare more complex non-linear functions (using a second degree fractional

polynomial function FP2) to simpler non-linear functions (using a first degree fractional polynomial function, FP1) and a linear function.

Internal validation

Apparent model performance will be quantified using the R^2 statistic and calibration plots (and associated measures such as calibration slope and calibration-in-the-large) estimated in the model development dataset (33). Optimism due to potential overfitting will then be checked and adjusted for using an internal validation approach via bootstrapping.. We will obtain 1000 bootstrap samples (each the same size as the original dataset) by sampling (with replacement) individuals from the original dataset. Then, to examine potential overfitting and produce optimism-adjusted performance estimates, in each bootstrap sample, a new model will be produced using the same process (e.g. backwards selection) as above, and the model's predictive performance then evaluated on the original sample. The average difference in the bootstrap models' apparent performance (in the bootstrap sample) and the test performance (in the original dataset) provide the optimism for each performance measures. Optimism-adjusted estimates of performance will then be derived by subtracting the optimism estimates from the original apparent performance estimates for the original model. Finally, shrinkage will be applied to correct for overfitting by multiplying the original model's beta regression coefficients (predictor effects in the original model) by a uniform shrinkage factor (equal to the optimism-adjusted calibration slope) and by then re-estimating the intercept to ensure overall calibration-in-the-large whilst constraining the revised predictor effects at their shrunken value. (33). This will give the final model.

Regression coefficients along with standard errors and 95% confidence intervals will be reported for the original (pre-shrinkage) model. Regression coefficients alone will be reported for the final shrunken model. Performance measures will be reported with 95% confidence intervals for the apparent performance as well as estimates of optimism-corrected performance from the internal validation.

For comparison, a full model forcing in all candidate prognostic factors will be produced avoiding backwards selection, with otherwise the same process of model development and internal validation as described above. Also, a model developed using a multivariate linear regression accounting for the correlation of outcome values at 6, 12 and 24 weeks will be considered.

Prognostic models for secondary outcomes (objective 4)

Model development for physical function at 6 weeks will follow the same strategy as for the primary outcome of leg pain intensity described above. For recovery at 6 weeks and surgery or further ESI at 24 weeks, which are both binary outcomes, logistic regression models will be used instead of linear regression models. For these two logistic models, discrimination will be assessed (using the C-statistic) in addition to calculating measures of calibration, and clinical utility assessed using net benefit and decision curves, with the range of important risk thresholds pre-defined based on consultation with clinicians and patients.

Missing data

Missing data will be summarised as frequencies and proportions for each variable. Multiple imputation will be used to handle missing data, using multivariate imputation by chained equations and assuming data are missing at random. Reasons for the missing values will be explored to investigate whether the missing at random assumption is reasonable. The number of imputations will be selected to correspond to the proportion of individuals with any missing data (38) and all variables considered for inclusion in the prognostic model will be included in the imputation model,

as well as including the outcome variables. Rubin's rules will be used to combine estimates across imputations (39).

Leg pain trajectories (objective 5)

Latent class growth analysis (40, 41) will be used to identify distinct groups (clusters) of participants with similar trajectories of leg pain intensity using weekly leg pain data form text message responses. Analysis will use those with baseline plus at least two follow-up measures within the three-month timeframe. Appropriate polynomial functional form for each trajectory will be chosen and statistical indices used to assess model fit will include the Bayesian Information Criterion and bootstrapped likelihood ratio test. Participants will be assigned to trajectories according to maximum probability assignment principle (42). Baseline patient characteristics associated with membership of each trajectory and treatment will be described.

Outcomes and prognostic factors in ESI and non-ESI subgroups (objective 6)

Some individuals decline a referral for an ESI, are referred but recover while on the waiting list, or choose to have other treatments such as surgery. To explore whether the effects of some prognostic factors differ in individuals who have an ESI and those that do not, we will use the combined dataset of both ESI and non-ESI patients, if there are sufficient participants recruited in the non-ESI pathway. A cohort of approximately 90 non-ESI participants will be large enough to explore the interaction between factors identified in the final ESI prognostic model and treatment outcomes.

A linear regression model for 6-week leg pain intensity will be fitted that includes the linear combination of predictor effects from the model derived for objective 3 as a predictor, treatment (ESI vs no-ESI) and an interaction term between the linear predictor and treatment. If this interaction is significant, further exploration of interactions between individual predictors and treatment will be undertaken. If the interaction is not significant, this would suggest they are generic predictive factors and not to do with treatment (i.e. treatment moderators). This will be exploratory analysis as the sample size is not powered for this analysis.

Patient and Public Involvement

We have adopted the approach advocated by INVOLVE Standards for Patient and Public involvement (PPIE). Patients' experiences of referral for an ESI and subsequent outcomes post ESI helped inform the research idea and study design. PPIE input has helped tailor the recruitment strategy and will be key to sharing results and brainstorming dissemination and future implementation ideas and strategies. A consensus workshop is planned with patients and clinicians to discuss the research findings and how they might progress to develop into a clinical tool. Members of the POiSE PPIE group will help interpret the study findings from a patient perspective; advising on how best to publicise the study findings to the wider public and supporting the design of evidence-based information materials (e.g. leaflets, online tools, patient stories) for clinicians and patients to use when considering ESI as a management option for disc-related sciatica.

Ethics and Dissemination

The POiSE study has received ethical approval (South Central Berkshire B Research Ethics Committee 21/SC/0257). Findings of the POiSE study will be presented at national and international conferences and published in peer reviewed journals. Once the results of the study have been published, further dissemination will be shared with the wider public, guided by PPIE advise.

After publication of the results of the cohort study, depersonalised datasets will be available upon request from primarycare.datasharing@keele.ac.uk.

Study status

Patient recruitment and follow-up is expected to continue until the end of 2024. Recruitment has started with more than 280 patients recruited by September 2023. The study is no longer recruiting additional NHS spinal sites to identify eligible patients.

Registration details

Research Registry www.researchregistry.com: UIN: researchregistry6844

Author Contributions

SS conceived the study. NF, RR, KK, RO and JO'D helped SS shape the fellowship application to secure funding for the POiSE study. SS led the design of the study with the support of her mentorship team NF, KK, RR, KS, RO and JO'D. RR and KS prepared the analysis plan. ND and SS will perform the analysis, supported by KS. AC and SS are responsible for project management and coordination activities of the study and ND is contributing to data monitoring and reporting. SS prepared the draft of the manuscript which all authors critically reviewed and approved the final version.

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Competing interests statement

None declared

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