Multi-centre randomised control trial comparing the clinical and cost effectiveness of trans-foraminal epidural steroid injection to surgical microdiscectomy for the treatment of chronic radicular pain secondary to prolapsed intervertebral disc herniation: NErve Root Block VErsus Surgery (NERVES)

Eudract No: 2014-002751-25

ISRCTN: 04820368

Statistical Analysis Plan: Final Analysis version v2.0 25/06/2019

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Dannii Clayton	Barbara Arch	Ashley Jones
Title	Independent Trial Statistician	QC Statistician	Independent Senior Statistician
Date	25/06/2019		
Protocol Version and Date	Version 7.0 25/10/2017		

1. Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Date changed
V7.0	2.0	17.4.1.1	Addition of details explaining how to derive questionnaire completion dates and when to exclude patients from the analysis.	24/06/2019
V7.0	2.0	17.4.5.2	Updated analysis details. After undertaking blind review on the data, the Likert score was found to be non-normal and therefore a Mann-Whitney U test will be carried out rather than the originally planned T-Test.	24/06/2019
V7.0	2.0	19	Added in additional analysis details.	24/06/2019
V7.0	2.0	20.2	Additional safety details.	24/06/2019
V7.0	2.0	17.4.2.1, 17.4.3.1, 17.4.4.1, 17.4.6.1, 17.4.7.1	Addition of details explaining how to derive missing questionnaire completion dates.	24/06/2019

2. Approval and agreement

At a minimum two versions of the SAP should be approved and stored within the statistics trial file.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: _____

Trial Statistician* [Trial statistician has seen unblinded data so has not written this SAP. Duty delegated to independent statistician who has not seen unblinded data.]

Name _____

Signed _____ Date _____

Senior Statistician* [Senior statistician has seen unblinded data so has not written this SAP. Duty delegated to independent statistician who has not seen unblinded data.]

Name _____

Signed _____ Date _____

Chief Investigator/clinical lead

Name _____

Signed _____ Date _____

3. Roles and responsibilities

Ashley Best (Department of Biostatistics, University of Liverpool), Trial Statistician; Dannii Clayton (Department of Biostatistics, University of Liverpool), Independent Statistician; Girvan Burnside (Department of Biostatistics, University of Liverpool), Senior Statistician; Ashley Jones (Department of Biostatistics, University of Liverpool), Independent Senior Statistician; Martin Wilby (The Walton Centre, Liverpool), Chief Investigator.

Author's contributions

D. Clayton proposed the statistical analysis plan and drafted the manuscript. A. Jones read, amended and approved the statistical analysis plan.

4. List of abbreviations and definitions of terms

AR	Adverse reaction
CRF	Case report form
ODQ	Oswestry Disability Questionnaire
IDSMC	Independent Data and Safety Monitoring Committee
COMI	Core Outcome Measures Index
RCT	Randomised Control Trial
SAE	Serious adverse event
TFESI	Transforaminal Epidural Steroid Injection
PID	Prolapsed Intervertebral Disc
QOL	Quality Of Life
CTRC	Clinical Trials Research Centre
QALY	Quality Adjusted Life Year
EudraCT	European Union Drug Regulating Authorities Clinical Trials

Contents

1. Change Control 1
2. Approval and agreement 2
3. Roles and responsibilities 3
4. List of abbreviations and definitions of terms 4
5. Statement of Compliance 7
6. Background and Rationale 8
7. NERVES Study Objectives 8
8. Investigational Plan and Study Design 8
   8.1. Overall study design and plan- description 8
   8.2. Treatments studied 8
   8.3. Treatment compliance 9
   8.4. Patient population studied 9
   8.5. Inclusion criteria 9
   8.6. Exclusion criteria 9
   8.7. Removal of patients from therapy or assessment 9
   8.8. Consent process 10
   8.9. Blinding 10
   8.10. Method of assignment to treatment 10
   8.11. Sequence and duration of all study periods 10
   8.12. Schedule of assessments 10
9. Listing of Outcomes 10
   9.1. Primary outcome 10
   9.2. Secondary outcomes 11
10. Determination of Sample Size 11
11. Study Framework 11
12. Confidence Intervals, p-values and Multiplicity 11
13. Timing and Objectives of Interim and Final Analyses 12
   13.1. Interim monitoring and analyses 12
   13.2. Final analysis 12
14. Disposition of Participants 12
   14.1. Screening, eligibility and recruitment 12
   14.2. Post randomisation discontinuations 13
15. Protocol Deviations 13
16. Unblinding 13
17. Efficacy Evaluations 13
   17.1. Data Sets Analysed 13
   17.2. Demographic and Other Baseline Characteristics 14
   17.3. Compliance with treatment 15
   17.4. Analysis of outcomes 15
   17.4.1 Primary Outcome 15
   17.4.1.1 Derivation 15

17.4.1.2 Analysis 19
17.4.2 ODQ at 30, 42 and 54 weeks after randomisation 19
17.4.2.1 Derivation 19
17.4.2.2 Analysis 19
17.4.3 Numerical rating scores for leg pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation 20
17.4.3.1 Derivation 20
17.4.3.2 Analysis 20
17.4.4 Numerical rating scores for back pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation 20
17.4.4.1 Derivation 20
17.4.4.2 Analysis 21
17.4.5 Likert Scale to assess patient treatment satisfaction at 54 weeks after randomisation 21
17.4.5.1 Derivation 21
17.4.5.2 Analysis 21
17.4.6 Modified Roland-Morris outcome score for sciatica at baseline, and at 18, 30, 42 and 54 weeks after randomisation 22
17.4.6.1 Derivation 22
17.4.6.2 Analysis 22
17.4.7 Core Outcome Measures Index (COMI) at baseline, and at 18, 30, 42 and 54 weeks after randomisation 22
17.4.7.1 Derivation 22
17.4.7.2 Analysis 24
17.4.8 Work status at follow-up 24
17.4.8.1 Derivation 24
17.4.8.2 Analysis 24
17.4.9 Cost-effectiveness, expressed as the incremental cost per quality-adjusted life-year (QALY) based on the EQ-5D-5L 24
17.4.9.1 Derivation 24
17.4.9.2 Analysis 24
18 Missing data and withdrawals 25
19 Additional analyses 25
20 Safety Evaluations 26
20.1 Data sets analysed 26
20.2 Presentation of the data 26
22 References 27

5. Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned **final** analyses for the study "NErve Root Block VErsus Surgery (NERVES)". The planned statistical analyses described within this document are compliant with those specified in brief within the NERVES protocol version 7.0 dated 25/10/2017.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These planned analyses will be performed by the trial statistician.

This study is a clinical trial of a medicinal product and is registered on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database. The statistical analysis plan has been developed to support the posting of results on the EudraCT system. This is a regulatory requirement which should be fulfilled within 6 months after the end of the study as defined within the clinical trial protocol.
The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001: Statistical Analysis and Reporting.

6. Background and Rationale

The rationale for the trial is outlined in the protocol. To summarise, both epidural steroid injections and surgical procedures are currently being used to remove herniated lumbar disc prolapses for sciatica. There currently exists no care pathway in the NHS that suggests any particular treatment and no comparison between surgical microdiscectomy and transforaminal epidural steroid injection exists. The trial is needed as potential health and economic gains are unlikely to be realised without robust evidence from an RCT. Clear evidence is required on the effectiveness and cost-effectiveness of Transforaminal Epidural Steroid Injection (TFESI) and surgical microdiscectomy.

7. NERVES Study Objectives

The objective of this trial is to compare the clinical effectiveness of TFESI for acute sciatica secondary to prolapsed intervertebral disc (PID) and surgical microdiscectomy.

The secondary objectives are:

1. To compare the cost effectiveness of TFESI and microdiscectomy for the treatment of sciatica secondary to PID.
2. To compare quality of life (QOL) outcomes for both treatments.

8. Investigational Plan and Study Design

8.1. **Overall study design and plan- description**

NERVES is a two-arm, multi-centre, phase III, randomised trial comparing the clinical and cost effectiveness of trans-foraminal epidural steroid injection to surgical microdiscectomy for the treatment of chronic radicular pain secondary to prolapsed intervertebral disc herniation. The trial includes an internal pilot involving two centres (Liverpool [Walton Centre] and Manchester [Salford Royal]), with an expected recruitment of 30 participants over 6 months. Full details can be found in section 9 of the protocol.

8.2. **Treatments studied**

The two treatments studied in NERVES are Transforaminal Epidural Steroid Injection (TFESI) and Surgical Microdiscectomy.

Dosing and administration details can be found in section 7 of the protocol.

8.3. **Treatment compliance**

Compliance with the randomised study intervention will be monitored by the CTRC through completion of case report forms at site recording the intervention given and the allocation provided by the online randomisation system. Any deviations from the randomised intervention will be explored with site.

During the follow-up patients may require further clinical intervention, which is permitted without the patient having to withdraw. Details of the treatment received and the reason for treatment will be collected. If patients crossover prior to receiving their initial treatment allocation then this should be recorded, with a reason, on the CRF “Form 3: Treatment Form”.

The number of patients who start on either treatment (arm A or B) and go on to receive the alternative treatment should be reported in a way that shows:

- The number of patients who started on TFESI and switched to surgical microdiscectomy
- The number of patients who started on surgical microdiscectomy and switched to TFESI
- The number of patients who were allocated to and received TFESI only
- The number of patients who were allocated to and received surgical microdiscectomy only
- The number of injections received by i) patients on the TFESI treatment only, and ii) patients receiving surgery and TFESI

8.4. **Patient population studied**

148 males and females between the age of 16 and 65, who present with sciatica that fail to respond to at least one form of non-operative treatment will be entered into NERVES. Those patients who have a serious neurological deficit, have not attempted any form of conservative treatment, are pregnant, have had previous spinal surgery at the same intervertebral disc and have a contraindication for surgery and/or injection are excluded.

8.5. **Inclusion criteria**

The inclusion criteria can be found in section 5 of the protocol.

8.6. **Exclusion criteria**

The exclusion criteria can be found in section 5 of the protocol.

8.7. **Removal of patients from therapy or assessment**

Due to the nature of both treatment arms removal of patients from therapy is not possible.

8.8. **Consent process**

Consent will be obtained after the investigator has explained the research study to the participant, emphasising that participation in the trial is voluntary and that the participant may withdraw at any stage of the trial for any reason. Consent will be sought at the initial clinical visit before randomisation.

8.9. **Blinding**

NERVES is an open label trial and the investigators and patients will not be blind to allocated treatments.

8.10. **Method of assignment to treatment**

Full details of the randomisation procedure can be found in section 6.3 and 9.2 in the protocol. Participants are randomised to treatment groups in a ratio of 1:1 using an online web randomisation system. Randomisation will be stratified by centre.

8.11. **Sequence and duration of all study periods**

A schematic of the study design can be found in section 1 of the protocol. Details of follow-up visits can be found in section 8.1.

To summarise this information, patients presenting with sciatica will be screened using inclusion and exclusion criteria. Once the patient has been assessed as eligible, consent will be sought. The patient is then entered into NERVES and randomised to either transforaminal epidural steroid injection or microdiscectomy and the treatment is administered. Participants will be asked to complete the ODQ, modified Roland-Morris outcome score, core outcome measures index, EQ-5D-5L and numerical rating score for leg and back pain at baseline, 18, 30, 42 and 54 weeks after randomisation.

8.12. **Schedule of assessments**

A full schedule of trial assessments and timeline of data collection can be found in section 8.1 of the protocol.

9. Listing of Outcomes

9.1. **Primary outcome**

The primary outcome is the Oswestry Disability Questionnaire (ODQ) at 18 weeks after randomisation (approximately 3 months post treatment).

9.2. **Secondary outcomes**

The secondary outcomes are:

1. ODQ at 30, 42 and 54 weeks after randomisation.
2. Numerical rating scores for leg pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation.
3. Numerical rating scores for back pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation.
4. Likert Scale to assess patient treatment satisfaction at 54 weeks after randomisation.
5. Modified Roland-Morris outcome score for sciatica at baseline, and at 18, 30, 42 and 54 weeks after randomisation.
6. Core Outcome Measures Index (COMI) at baseline, and at 18, 30, 42 and 54 weeks after randomisation.
7. Work status (return to work and work days lost if applicable).
8. Cost-effectiveness, expressed as the incremental cost per quality-adjusted life-year (QALY) based on the EQ-5D-5L.

10. Determination of Sample Size

The sample size calculation can be found in section 9.4 of the protocol.

11. Study Framework

The overall objective for each of the study outcomes is to compare Transforaminal Epidural Steroid Injection (TFESI) with surgical microdiscectomy for superiority.

12. Confidence Intervals, p-values and Multiplicity

All applicable statistical tests will be two-sided and will be performed using a 5% significance level; 95% confidence intervals will be presented. No adjustment will be made for multiplicity for the secondary outcomes.

13. Timing and Objectives of Interim and Final Analyses

13.1. **Interim monitoring and analyses**

Details on interim analyses are compatible with those found in the protocol in section 9.5. The IDSMC met at least annually to review the accumulated data. Details can be found in the Statistical Analysis Plan: Internal Pilot version 1.0 dated 09/07/15.

13.2. **Final analysis**

The final analysis for all outcomes will be analysed after the end of the trial, which is defined in section 8.7 of the protocol as “the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database”.

14. Disposition of Participants

14.1. **Screening, eligibility and recruitment**

Screening logs will be summarised by site in a table detailing:

i) the number of patients who were assessed for eligibility at the screening visit,
ii) those who met the study inclusion criteria at screening (expressed as a frequency and a % with the denominator being i),
iii) those who did not meet the study inclusion criteria at screening (expressed as a frequency and a % with the denominator being i),
iv) those who were eligible at screening and consent obtained, (expressed as a frequency and a % with the denominator being ii),
v) those who were eligible at screening and consent not obtained, (expressed as a frequency and a % with the denominator being ii),
vi) those who provided consent but were not randomised (expressed as a frequency and a % with the denominator being iv),
vii) those who provided consent and were randomised (expressed as a frequency and a % with the denominator being iv),

Reasons for ineligibility will be summarised by site and overall in a table with reasons. Frequencies will be presented along with percentages using the denominator as iii).

Reasons for consent declined will be summarised by site and overall in a table using categories. Frequencies will be presented along with percentages using the denominator as v).

A recruitment summary table will be presented showing the following for each centre: centre code, hospital name, dates site opened/closed to recruitment, dates of first/last randomisation and total number randomised.

14.2. **Post randomisation discontinuations**

Ideally, patients that decide to withdraw from treatment prior to treatment will remain in the study for follow-up. However, patients could decide to withdraw from the trial completely. Withdrawals will be presented as line listings detailing:

- Randomisation number
- Date of withdrawal
- Date of visit
- Date of discontinuation and whether before/after treatment
- Level of withdrawal
- Who made the decision to withdraw the participant from the trial
- How many injections the participant has received (if applicable)
- Reason for discontinuation

15. Protocol Deviations

Protocol deviations to be reported can be found in section 6 of the trial monitoring plan (V2.0 dated 25/01/2018).

16. Unblinding

Not applicable as NERVES is an open label study.

17. Efficacy Evaluations

17.1. **Data Sets Analysed**

The principle of intention-to-treat, as far as practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all randomised participants, in the group to which they were allocated, and for whom the outcome(s) of interest have been observed/measured.

The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given.

17.2. **Demographic and Other Baseline Characteristics**

The following patient baseline data will be presented:

- Gender (male/female)
- Age (EudraCT categories: Adolescents (12-17 years/ Between 18 and 65 years/ 65 years to 84 years)
- Whether the participant is of reproductive potential (yes/no)
- Whether the patient is currently taking coagulant medication (yes/no)
- Whether the patient has previously had surgery at the same intervertebral disc (level) (yes/no)
- How many weeks the patient has experience leg pain symptoms for
- Whether the patient has used medication to help treat pain and symptoms (yes/no)
- Whether the patient has modified daily activities to help pain and symptoms (yes/no)
- Whether the patient has attended physiotherapy to help pain and symptoms (yes/no)
- Whether the patient has had other conservative (non operative) treatment to help pain and symptoms (yes/no)
- Estimated volume of canal occupied by disc prolapse as shown on MRI scan (Less than 25%/ Between 25-50%/Greater than 50%)
- Weight (kg)
- Height (cm)
- Posture (normal/abnormal)
- Range of movement (normal/abnormal)
- Muscle strength (normal/abnormal)
- Ankle jerks present (left/right/yes/no)
- Knee jerks present (left/right/yes/no)
- SLR reduction present (yes/no)
- Whether the patient has any other abnormalities (yes/no)
- Whether the patient is currently employed (yes/no)
- Whether the patient is currently unable to attend work due to sciatica (yes/no)
- Whether the patient is currently taking analgesics, steroids or anticoagulant medication (yes/no)

The above baseline values can be found on CRF "Form 1: Baseline & Eligibility". For continuous variables the mean, SD, minimum, median, maximum and IQR will be presented to 1 decimal place.

17.3. **Compliance with treatment**

See section 8.1 of the NERVES trial protocol for definition of treatment compliance. The number and percentage of patients complying with treatment overall and by centre split by treatment group will be summarised.

17.4. **Analysis of outcomes**

All values for each outcome will be presented to 2 decimal places with the exception of p-values which will be presented to 3 decimal places.

17.4.1 Primary Outcome

Oswestry Disability Questionnaire (ODQ) at 18 weeks (± 6 weeks) (approximately 3 months post intervention).

17.4.1.1 Derivation

Missing completion dates

For the primary outcome analysis, we need to know if the ODQ was completed within the protocol specified window (18 +/- 6 week post randomisation). If the date is missing then the date should be estimated as follows:

- If the questionnaire is from a face-to-face follow up visit (W18, W54) and if the variable FBK1CMPC='Yes' (NERVES questionnaire (Booklet 1) completed by the patient?) then the date of the visit is taken as the date of questionnaire completion.
- If the above was not the case but there is a completed booklet 1, then the date will be estimated as the midpoint between the date the questionnaire was provided to the patient and the latest possible date receipt of the CRF at the CTU. This can be expressed as:

$$Completion\ Date = Date\ provided + \frac{Date\ received - Date\ provided}{2}$$

- If the date is entered onto the questionnaire but is before the randomisation date (except for baseline questionnaires) then this should be imputed as above.

Note: If there are duplicate CRFs then the latest of these dates will be used.

Scoring

Scores from the ODQ can be found in patient questionnaire booklet 1. Scores will be calculated following the guidelines outlined in [10]. Scores are obtained as follows.

Step 1: Recode the 10 ODQ items

Items 1-10 on the ODQ will be recoded as in Table 17.4.1.1(a).

Step 2: Calculate the overall score (%)

$$\text{Overall ODQ score} = \frac{\text{Sum of the score of each of the applicable items with a non missing answer}}{\text{Maximum possible score}} \times 100$$

(Where the maximum possible score is based on the number of questions answered.)

Step 3: Interpret the overall score (%)

Interpreted as in Table 17.4.1.1(b)

Note: If a patient has not completed the questionnaire at 18 ± 6 weeks post randomisation or has answered less than 8 out of 10 questions (including item 8), then the patient should be excluded from the analysis.

Table 17.4.1.1(a): ODQ Recoding items

Item no (MACRO variable)	Recoding
ODQS01C	0 = I have no pain at the moment. 1 =The pain is very mild at the moment. 2 =The pain is moderate at the moment. 3 =The pain is fairly severe at the moment. 4 = The pain is very severe at the moment. 5 =The pain is the worst imaginable at the moment.
ODQS02C	0 = I can look after myself normally without causing extra pain. 1 = I can look after myself normally but it is very painful. 2 = It is painful to look after myself and I am slow and careful. 3 = I need some help but manage most of my personal care. 4= I need help every day in most aspects of self-care.

	5 = I do not get dressed, wash with difficulty and stay in bed.
ODQS03C	0 = I can lift heavy weights without extra pain. 1 = I can lift heavy weights but it gives extra pain. 2 = Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned. 3 = pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned. 4 = I can lift only very light weights. 5 = I cannot lift or carry anything at all.
ODQS04C	0 = Pain does not prevent me walking any distance. 1 = Pain prevents me walking more than one mile. 2 = Pain prevents me walking more than a quarter of a mile. 3 = Pain prevents me walking more than 100 yards. 4 = I can only walk using a stick or crutches. 5 = I am in bed most of the time and have to crawl to the toilet.
ODQS05C	0 = I can sit in any chair as long as I like. 1 = I can sit in my favourite chair as long as I like. 2 = Pain prevents me from sitting for more than 1 hour. 3 = Pain prevents me from sitting for more than half an hour. 4 = Pain prevents me from sitting for more than 10 minutes. 5 = Pain prevents me from sitting at all.
ODQS06C	0 = I can stand as long as I want without extra pain. 1 = I can stand as long as I want but it gives me extra pain. 2 = Pain prevents me from standing for more than 1 hour. 3 = pain prevents me from standing for more than half an hour. 4 = Pain prevents me from standing for more than 10 minutes. 5 = Pain prevents me from standing at all.
ODQS07C	0 = My sleep is never disturbed by pain. 1 = My sleep is occasionally disturbed by pain. 2 = because of pain I have less than 6 hours sleep.

	3 = Because of pain I have less than 2 hours sleep. 4 = Because of pain I have less than 2 hours sleep. 5 = Pain prevents me from sleeping at all.
ODQS08C	0 = My sex life is normal and causes no extra pain. 1 = My sex life is normal but causes some extra pain. 2 = My sex life is nearly normal but is very painful. 3 = My sex life is severely restricted by pain. 4 = My sex life is nearly absent because of pain. 5 = Pain prevents any sex life at all.
ODQS08NC	1 = Section 8 is not applicable to me.
ODQS09C	0 = My social life is normal and causes me no extra pain. 1 = My social life is normal but increases the degree of pain. 2 = Pain has no significant effect on my social life apart from limiting my more energetic interests. 3 = Pain has restricted my social life and I do not go out as often. 4 = Pain has restricted social life to my home. 5 = I have no social life because of pain.
ODQS10C	0 = I can travel anywhere without pain. 1 = I can travel anywhere but it gives extra pain. 2 = pain is bad but I manage journeys over two hours. 3 = pain restricts me to journeys of less than one hour. 4 = pain restricts me to short necessary journeys under 30 minutes. 5 = Pain prevents me from travelling except to receive treatment.

Table 17.4.1.1(b): ODQ Interpretation

The ODQ overall percentage corresponds to the categories below.

0% to 20%: Minimal disability	The patient can cope with most living activities. Usually no treatment is indicated apart from advice on lifting sitting and exercise.
21% to 40%: Moderate disability	The patient experiences more pain and difficulty with sitting, lifting and standing.

	Travel and social life are more difficult and they may be disabled from work. Personal care, sexual activity and sleeping are not grossly affected and the patient can usually be managed by conservative means.
41% - 60%: Severe disability	Pain remains the main problem in this group but activities of daily living are affected. These patients require a detailed investigation.
61%-80%: Crippled	Back pain impinges on all aspects of the patient's life. Positive intervention is required.
81%-100%	These patients are either bed-bound or exaggerating their symptoms.

17.4.1.2 Analysis

ODQ score at 18 weeks post-randomisation will be compared between groups using a linear regression model, adjusting for the stratification variable centre, treatment group and baseline ODQ score. The mean(SD) ODQ score at baseline and 18 weeks will be presented. The mean difference and 95% CI in ODQ at 18 weeks will be presented along with a p-value for the treatment covariate at 18 weeks. Model assumptions will be tested by checking for normality.

17.4.2 ODQ at 30, 42 and 54 weeks after randomisation

17.4.2.1 Derivation

Derivation details, including details on how to derive missing questionnaire completion dates, can be found in section 17.4.1.1.

17.4.2.2 Analysis

Change from baseline summary statistics (Total [n], Mean, SD, median, interquartile range, minimum and maximum) will be presented split by treatment arm at four key time-points(T18, T30, T42 and T54) using visit windows as specified in the protocol. Only data from scheduled visits at these time-points will be included within the summary statistics.

A repeated measures random effects model will be fitted. The dependent variable will be post baseline ODQ. Covariates will be: baseline ODQ, treatment arm, time (fitted as a continuous

variable), and a time-treatment arm interaction. Centre will be fitted as a random effect. The time-treatment interaction can be dropped if it is found to be non-significant ($p<0.05$).

If the model contains a time-treatment interaction, the mean (SD) ODQ for each treatment arm and the mean difference between treatment arms in ODQ will be estimated from the model, for each key time-point (T30, T42 and T54), together with a 95% CI.

If the model contains no interaction, the treatment effect (estimated mean difference in ODQ) will be reported together with a 95% CI and a p-value.

Note: whilst the study design defines ODQ to be measured a specific time-points, measurements that are not taken at per-protocol time-points may be included in this mixed model analysis.

17.4.3 Numerical rating scores for leg pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation

17.4.3.1 Derivation

Numerical rating scores for leg pain at baseline can be found in patient questionnaire booklet 1. This is a continuous outcome that gives a numerical rating between 1 and 100 denoting the severity of the pain, where 0 and 100 denote “no pain” and “worst pain you can imagine” respectively. The MACRO variable name is NUMRATBI and takes a value between 1 and 100. The date that the patient questionnaire (booklet 1) has been completed is also required for this outcome; see section 17.4.1.1 for details on how to derive missing questionnaire completion dates.

17.4.3.2 Analysis

For this outcome see section 17.4.2.2 for analysis details. In addition to this, effect estimates, 95% CIs and a p-value at T18 should be reported.

17.4.4 Numerical rating scores for back pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation

17.4.4.1 Derivation

Numerical rating scores for back pain at baseline can be found in patient questionnaire booklet 1. This is a continuous outcome that gives a numerical rating between 1 and 100 denoting the severity of the pain, where 0 and 100 denote “no pain” and “worst pain you can

imagine", respectively. The MACRO variable name is NUMRATAI and takes values between 1 and 100. The date that the patient questionnaire (booklet 1) has been completed is also required for this outcome; see section 17.4.1.1 for details on how to derive missing questionnaire completion dates.

17.4.4.2 Analysis

For this outcome see section 17.4.2.2 for analysis details. In addition to this, effect estimates, 95% CIs and a p-value at T18 should be reported.

17.4.5 Likert Scale to assess patient treatment satisfaction at 54 weeks after randomisation

17.4.5.1 Derivation

Scores from the Likert Scale can be found from questions 6 and 7 of the COMI. The COMI score is calculated by recoding responses as in Table 17.4.5.1(a) and taking the average of both items. This score should only be calculated if all items are present.

Table 17.4.5.1(a)

Item no (MACRO variable)	Recoding
COMI6C	1= Very satisfied 2 = Somewhat satisfied 3 = Neither satisfied nor dissatisfied 4 = Somewhat dissatisfied 5 = Very dissatisfied
COMI7C	1= Very satisfied 2 = Somewhat satisfied 3 = Neither satisfied nor dissatisfied 4 = Somewhat dissatisfied 5 = Very dissatisfied

17.4.5.2 Analysis

Patient treatment satisfaction scores at 54 weeks will be compared between groups using the Mann-Whitney U test. A blind review of the data was undertaken and the distribution of the Likert score at 54 weeks was found to be non-normal. The mean difference (along with a 95% confidence interval), test-statistic and p-value will be presented. Summary statistics (mean, SD and range) will also be presented for each treatment group.

17.4.6 Modified Roland-Morris outcome score for sciatica at baseline, and at 18, 30, 42 and 54 weeks after randomisation

17.4.6.1 Derivation

Modified Roland-Morris scores can be found in patient questionnaire booklet 1. The score is obtained by adding up the number of items the patient has ticked. Scores can vary between 0 and 24 and greater levels of disability are reflected by higher scores [11]. The MACRO variable names for each of the statements on the form are MODRM01C, MODRM02C, MODRM03C, MODRM04C, MODRM05C, MODRM06C, MODRM07C, MODRM08C, MODRM09C, MODRM10C, MODRM11C, MODRM12C, MODRM13C, MODRM14C, MODRM15C, MODRM16C, MODRM17C, MODRM18C, MODRM19C, MODRM20C, MODRM21C, MODRM25C, MODRM26C and MODRM27C. Any of the variables selected by the patient should be recoded to “1” and all variables not selected recoded to “0”. The date that the patient questionnaire (booklet 1) has been completed is also required for this outcome; see section 17.4.1.1 for details on how to derive missing questionnaire completion dates.

17.4.6.2 Analysis

For this outcome see section 17.4.2.2 for analysis details. In addition to this, effect estimates, 95% CIs and a p-value at T18 should be reported.

17.4.7 Core Outcome Measures Index (COMI) at baseline, and at 18, 30, 42 and 54 weeks after randomisation

17.4.7.1 Derivation

Core Outcome Measures Index scores can be found in patient questionnaire booklet 1 (Questions 1-5). Pain intensity, function and symptom-specific and general well-being are measured using a 1-5 point Likert scale. Disability measurements for social life and work are measured in days of work incapacity/restricted activity over the past 4 weeks and could range from 0 to 28. The COMI score is calculated by recoding responses as in Table 17.4.7.1(a) and taking the average of all items. COMI scores should only be calculated if all items are present.

The date that the patient questionnaire (booklet 1) has been completed is also required for this outcome; see section 17.4.1.1 for details on how to derive missing questionnaire completion dates.

Table 17.4.7.1(a)

Item no (MACRO variable)	Recoding
COMI1AC	1= Not at all bothersome 2 = Slightly bothersome 3 = Moderately bothersome 4 = Very bothersome 5 = Extremely bothersome
COMI1BC	1 = Not at all bothersome 2 = Slightly bothersome 3 = Moderately bothersome 4 = Very bothersome 5 = Extremely bothersome
COMI2C	1 = Not at all 2 = A little bit 3 = Moderately 4 = Quite a bit 5 = Extremely
COMI3C	1 = Very dissatisfied 2 = Somewhat dissatisfied 3 = Neither satisfied nor dissatisfied 4 = Somewhat satisfied 5 = Very satisfied
COMI4I	1 = 0 days 2 = 1-7 days 3 = 8- 14 days 4 = 15-21 days 5 = > 22 days
COMI05I	1 = 0 days 2 = 1-7 days 3 = 8- 14 days 4 = 15-21 days 5 = > 22 days

17.4.7.2 Analysis

For this outcome see section 17.4.2.2 for analysis details. In addition to this, effect estimates, 95% CIs and a p-value at T18 should be reported.

17.4.8 Work status at follow-up

17.4.8.1 Derivation

This includes information found on CRF "Form 1: Baseline & Eligibility" on page 3 and CRF "Form 4: Follow up visits" on page 1. If a patient was unable to attend work at baseline and the date they stopped and returned to work at baseline and follow-up respectively is stated, then the number of work days lost under the assumption each patient works 5 out of 7 days per week should be calculated.

17.4.8.2 Analysis

Firstly, a summary of the following will be presented:

- number of patients that are employed/not employed at each time point by treatment group (Baseline, week 18 and week 54)
- of those patients who are employed, the number of patients that are off work/at work by treatment group
- of those patients who are employed and unable to work, the number of patients that returned to work at 18 and 54 weeks
- Mean, SD, median, IQR and range of the work days lost where applicable

Secondly, work status (at work or off work) at 18 or 54 weeks post randomisation will be compared between groups using a chi-square test. The chi-square statistic and p-value will be presented. In addition to this, the relative risk and 95% confidence interval will be presented.

17.4.9 Cost-effectiveness, expressed as the incremental cost per quality-adjusted life-year (QALY) based on the EQ-5D-5L

17.4.9.1 Derivation

This is a health outcome and will not be discussed in the SAP as the analyses will be undertaken by the trial health economist.

17.4.9.2 Analysis

This will be included in the health economic SAP as mentioned in section 19 [13].

18 Missing data and withdrawals

The numbers (with reasons) of losses to follow-up and withdrawals over the course of the trial will be summarised by treatment arm. The primary outcome is ODQ score at 18 weeks post-randomisation so if a patient withdraws after 18 weeks they will still contribute towards the primary analysis, given that consent to use all existing data collected up to that point is not removed.

The number of patients with missing data for the primary outcome and each secondary outcome will be presented in a table along with percentages.

Sensitivity analyses will be carried out if the amount of missing data is greater than 10%. Multiple imputation will be used to assess the robustness of the analysis to missing primary outcome data. The multiple imputation method will follow the guidelines set out in Jakobsen et al [14]. PROC MI in SAS will be used to generate 50 complete data sets. The imputation model will include all variables included in the primary outcome analysis model (treatment group, centre and baseline ODQ), and also ODQ measured at additional time points. The random seed for the imputation process will be pre-specified as 753. The complete data sets will be analysed using the model specified in section 17.4.1.2, and the results of all models combined using PROC MIANALYZE. The overall summary adjusted mean difference will be presented with 95% confidence intervals, to assess the sensitivity of the primary analysis to missing data.

19 Additional analyses

Health economics

The trial health economist will prepare a full economics analysis plan.

Additional analysis 1

As well as the model specified for our primary outcome analysis, we will also consider if any of the following baseline variables adjust our estimate of treatment effect by adding them to our mixed effects model as fixed effects:

- Age (Years)
- Sex (male/ female)
- BMI (KG /m^2)
- Duration of symptoms (weeks)

- Estimate volume of canal occupied by disc prolapse (Less than 25%, Between 25%-50%, Greater than 50%)

20 Safety Evaluations

20.1 Data sets analysed

For the safety analysis patients will be analysed according to which treatment was received in order to accurately represent the adverse effects of each treatment.

20.2 Presentation of the data

All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) reported by the clinical investigator will be presented in a table. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity (mild, moderate, severe) within each SOC term and preferred term. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by causality (possibly, probably, almost certainly) within each SOC term and preferred term. For each patient, only the maximum relationship experienced of each type of AE will be displayed. Note that for relationship to TFESI is reported as 3 separate components (Injection, steroid, anaesthetic) and these will be reported separately. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Adverse events will be categorised according to severity as “Mild”, “Moderate”, or “Severe”. They will also be classified in relation to the causality with the treatment as “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Almost certainly”. Full details on the definition and classification of these adverse events are presented in section 10 of the protocol. For the purpose of EudraCT, ARs, fatal SAEs, non-fatal SARs and fatal SARs will be presented in separate tables.

21 Quality Control

To ensure quality control, an independent statistician will follow this SAP to independently program the primary analysis and safety data from the raw data. Any discrepancies found will be discussed with the senior trial statistician to resolve. No programming will be shared or shown between the statisticians. The independent statistician will also check the report against their output obtained from the statistical software.

22 References

1. *International Conference on Harmonisation. Topic E3 Structure and content of clinical study reports. (CPMP/ICH/137/95). 1995*
2. *International Conference on Harmonisation. Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96). 1998.*
3. *Guidance on Statistical Analysis Plans.*
4. *Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. BMJ 2010;340:c332..*
5. *Shuster JJ: Diagnostics for assumptions in moderate to large simple clinical trials: do they really help? Stat Med 2005, 24(16):2431–2438.*
6. *Campbell H, Dean CB. The consequences of proportional hazards based model selection. Statistics in Medicine. 2013*
7. *Raab GM, Day S, Sales J: How to select covariates to include in the analysis of a clinical trial. Control Clin Trials 2000, 21(4):330–342.*
8. *Freeman PR: The performance of the two-stage analysis of two treatment, two-period crossover trials. Stat Med 1989, 8(12):1421–1432.)*
9. *Kahan BC: Bias in randomised factorial trials. Stat Med 2013, 32(26):4540–4549.*
10. *The Oswestry Disability Index : Fairbank, Jeremy. Spine Volume: 25 Issue 22 (2000) ISSN: 0362-2436 Online ISSN: 1528-1159*
11. *Roland, Martin, and Jeremy Fairbank. "The Roland–Morris disability questionnaire and the Oswestry disability questionnaire." Spine 25.24 (2000): 3115-3124.*
12. *Mannion, Anne F., et al. "The quality of spine surgery from the patient's perspective. Part 1: the Core Outcome Measures Index in clinical practice." European Spine Journal 18.3 (2009): 367-373.*
13. *Eifiona Wood and Professor Dyfrig Hughes, Health economics analysis plan for the NERVES trial*

14. *Jakobsen JC, Gluud C, Wettersley J and Winkel, P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol 2017;17:162.*