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)

Trial Protocol

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Study Sponsor(s):

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CTRC
Clinical Trials Research Centre

NHS
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General Information

This document describes the 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) trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Clinical Trials Research Centre (CTRC)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Clinical Trials Unit; MC CTU), epilepsy, oral health and obstetrics and gynaecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The NIHR Medicines for Children Research Network and National Cancer Research Network are part of the National Institute for Health Research Clinical Research Network.

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The contact details of other individuals involved in the trial are detailed in the Trial Oversight Committee Membership document.

Table of Contents

Glossary

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CHEME	Centre for Health Economics & Medicines Evaluations, Bangor University
COMI	Core Outcomes Measures Index
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
DSFC	Data Sharing Framework Contract
DSUR	Developmental Safety Update Report
EUDRACT	European Clinical Trials Database
ESI	Epidural Steroid Injection
GP	General Practitioner
HTA	Health Technology Assessment
HRA	Health Research Authority
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
MC CTU	Medicines for Children Clinical Trials Unit
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
ODQ	Oswestry Disability Questionnaire
PI	Principal Investigator
PID	Prolapsed Intervertebral Disc
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse N.B. When RN is referred to in this protocol it means either the research nurse or someone who has been delegated that duty
RSI	Reference Safety Information
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SNRI	Selective Nerve Root Injection
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFESI	Trans-Foraminal Epidural Steroid Injection
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

XR	X-Ray

1 PROTOCOL SUMMARY

Title:

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)

Phase:

III

Population:

148 patients

Inclusion criteria:

- Diagnosed lower extremity radiculopathy (sciatica)
- Sciatica secondary to prolapsed intervertebral disc (PID) (proven by MRI)
- Duration of symptoms between 6 weeks and 12 months
- Leg pain non-responsive to conservative, non-invasive management
- Age 16 – 65 years
- Patient has attempted at least one form of conservative (non-operative) treatment* but this has not provided adequate relief of patient's pain/symptoms
- Patient has provided written, informed consent

*including but not limited to; medication, physiotherapy, modification of daily activities

Exclusion criteria:

- Serious neurological deficit (e.g. foot-drop/possible cauda-equina compression)
- Previous spinal surgery at the same intervertebral disc (level)
- Sciatica presentation for longer than 12 months
- Age < 16
- Age > 65
- Patient has not attempted any form of conservative treatment
- Any patient who has a contraindication for surgery and/or injection
- Patient known to be pregnant

Study Centres and Distribution:

UK NHS out-patient neurosurgical, pain, and orthopaedic clinics (see Section 3)

Study Duration:

54-62 weeks per participant

Description of Agent/ Intervention:

The technologies to be compared are:

1. Fluoroscopically guided trans-foraminal epidural steroid injection (TFESI) of a standard combination of local anaesthetic and steroid drug

And

2. Standard surgical lumbar microdiscectomy

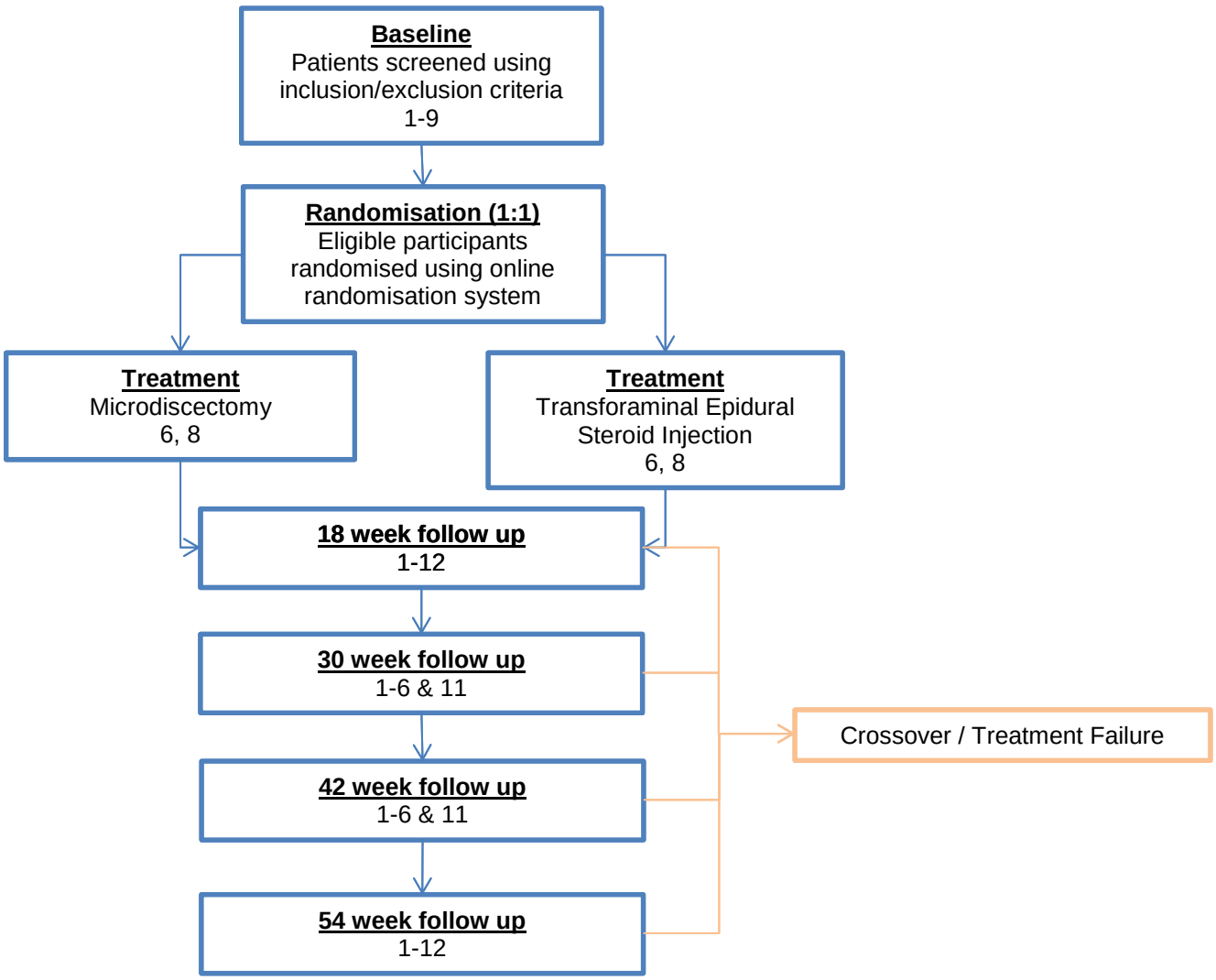
(see Section 7 for further information)

Primary Outcome:

Oswestry Disability Questionnaire (ODQ; a condition specific outcome measure with over 30 years of scientific validation) at 18 weeks (approximately 3 months post intervention)

Secondary Outcome/s:	Secondary outcomes include ODQ at 30, 42 and 54 weeks, numerical rating scores for leg and back pain, Likert scale assessing patient satisfaction, Modified Roland-Morris outcome score for sciatica, Core Outcome Measures Index (COMI), quality of life and health economic outcomes including work status

Schematic of Study Design



Trial-specific activities undertaken at each timepoint:

1. **Oswestry Disability Questionnaire (ODQ) (*primary outcome at 18 week follow up)***
2. Modified Roland-Morris outcome score for sciatica
3. Core Outcome Measures Index (COMI)
4. Numerical rating scores for leg and back pain
5. EQ-5D-5L
6. Resource Use Questionnaire (RUQ)
7. Physical examination
8. Pregnancy
9. Concomitant medications
10. Return to work
11. Treatment satisfaction (Likert scale)
12. Adverse events

2 BACKGROUND INFORMATION

2.1 Introduction

Sciatica can be described as a symptom rather than a diagnosis; it is broadly defined as leg pain in the distribution of a lumbosacral nerve root. Estimates of caseload vary substantially within the literature due to difficulties in definition and poor data capture. A UK epidemiological study suggests lifetime prevalence up to 43%, annual incidence of 5% and point prevalence up to 13% of the population at any one time. Other studies suggest a lifetime prevalence of low back pain over 80%, and that 10% of patients with back pain suffer sciatica as well. Over 90% of sciatica is due to a prolapsed intervertebral disc. Sciatica is a common condition affecting over 3% of the population at any one time (1). As patients affected are typically young, working adults it may be helpful to consider three categories of sciatica:

1. Acute sciatica – lasts less than 3 months and may be self-limiting with little or no impact on the patient's lifestyle
2. Chronic sciatica - persists beyond 3 months and has a tremendous impact upon the patient's lifestyle and working ability
3. Resistant sciatica – present for more than 12 months

Although the duration of pain may vary considerably, and the natural history of sciatica is favourable within one year, many patients have pain that persists beyond 6 weeks which could have considerable impact upon the employment market and patients' lives. It is generally accepted that pain persisting beyond 6 weeks is unlikely to get better imminently and would require further patient investigation and treatment. Treatment options include drugs, injections of drug combinations into the spine and surgical techniques to remove the prolapsed disc.
Spinal injection involves the administration of a mixture of local anaesthetic and steroid into the spine via one of three main routes; through the base of the spine (caudal epidural), through the back of the spine (inter-laminar) or through the nerve tunnel directly adjacent to the prolapsed disc (trans-foraminal epidural steroid injection (TFESI)). The latter mode is reported to be the most efficient and successful (2). Although this specific use of steroid is outside the marketing authorisation (off-label) it is commonly used and a widely accepted treatment for lower back pain. Of the surgical techniques, microdiscectomy to remove the prolapsed disc is considered the 'gold standard' with reported success rates of 90% (3). However, as sciatica has a natural history, there is potential that the treatment administered in the form of injection may render surgery as excessive.

There is currently no care pathway in the NHS that suggests any particular treatment, and no direct comparison exists between surgical microdiscectomy to treat sciatica secondary to lumber disc prolapse and nerve root blocks such as TFESI. This trial aims to address that by comparing surgical microdiscectomy to local steroid and anaesthetic administered accurately to the source of leg pain in terms against various outcomes.

2.2 Rationale

Sciatica is a common condition; in the UK (2010/2011) over 25,000 therapeutic epidural steroid injections were administered and over 9,000 surgical procedures to remove herniated lumbar disc prolapses were performed for sciatica (HES data). Case values estimated for the UK NHS are £600 per ESI and approximately £4,000 for surgical microdiscectomy (which has an average two nights in hospital per patient).

Previous studies of epidural steroid injections for sciatica
Epidural Steroid Injections (ESI) are known to improve patients' sciatica. A wide variety in practice exists across the UK in the methods of administration of the ESI.

ESI involve the administration of a mixture of local anaesthetic and steroid into the epidural space via one of three main routes; through the base of the spine (caudal epidural), through the back of the spine (inter-laminar) or through the nerve tunnel directly adjacent to the prolapsed disc (trans-foraminal). The most widely used injection therapy is epidural injection of steroids, by either the interlaminar route or the caudal route. Placing the needle through the bony tunnel through which the lumbar nerve root exits the spine can accurately place the drug closer to the target site. This routinely requires X-ray guidance or CT scanning guidance; most pain clinics in the UK are able to offer this treatment.

Although randomised controlled trials (RCTs) have been done looking at ESI for acute sciatica, these have not included comparisons between TFESI and inter-laminar ESI. However, prospective and case control studies have compared these and demonstrated a superior efficacy of TFESI (4-6). A comprehensive review of the literature has recently been published by the HTA (7). Only one small RCT ((8); n=100) has directly compared inter-laminar ESI to surgery for sciatica secondary to prolapsed intervertebral disc (PID) and suggested that ESI could prevent 50% of surgical interventions. One previous UK RCT (WEST study; (9); n= 228) funded by the HTA compared inter-laminar injection of steroid to placebo (injection of saline between the spinous processes) for patients with sciatica ranging from 4 weeks to 18 months and found no benefit of steroid injections beyond 3 weeks of follow up. Various other studies have shown that ESI only have a small short-term effect on leg pain and disability compared with placebo, and no effect in the long term (10). These poor medium to long term results have given ESI poor perceived efficacy and hence they are widely ignored in the treatment of acute sciatica.

The transforaminal mode (TFESI) of administration of the drug mixture into the epidural space, under fluoroscopic guidance, is reported to be the most successful in a prospective randomised study (compared to injection of saline or local anaesthetic in epidural space or intramuscular steroid or saline injection) and this is the route which will be considered in this study (11, 12). Relief of pain was corroborated by significant improvements in function and disability, and reductions in use of other health care.

TFESI is believed to be superior in efficacy to inter-laminar administration of ESI due to delivery of the drug closer and accurately to the site of the pathology/disc prolapse. A prospective study of TFESI ((5), n=48) for acute sciatica suggests long-term pain reduction in over 80% of patients. One recent RCT as mentioned above ((11); n=150) compared the outcomes of selective nerve root injection (SNRI) and local anaesthetic, local anaesthetic alone, or normal saline, and intramuscular injection of steroid or normal saline. The only radiological feature associated with successful outcome was the grade of nerve root compression. Of patients with low-grade root compression (n=71), 75% responded favourably to SNRI and avoided surgery by 12 months follow up.
Although little data exists directly comparing TFESI to inter-laminar steroid injections for sciatica, there are a number of on-going studies throughout the world at the recruitment stage specifically looking at this but are experiencing recruitment difficulties because of the lack of a surgical treatment arm. One recent study ((13); n=238) reported 65% of injections were effective at follow-up greater than 6 months (based on patient reported measures) suggesting that the administration of drug closer to the disc prolapse may improve efficacy when compared to other methods of administration.

Adverse events associated with SNRI procedures are rare, typically less than 1%, but can be severe and include paraplegia, infection, haematoma, intravascular injection of medication, direct nerve trauma, subdural injection of medication, air embolism, disc entry, urinary retention, radiation exposure, and hypersensitivity reactions.

The advantages of spinal injections are:

a) They are a relatively cheap and low risk procedure compared to surgery.

b) Success rates have been estimated to be as high as 75%.
c) They are delivered as a day case procedure requiring no hospital admission and can be easily repeated.
d) The range of treatment providers is large ranging from radiologists to surgeons or pain physicians.

The disadvantages of spinal injections are:
a) Their true success rate is largely unknown. They may work well in the short term, but patients may have their pain return after some weeks.
b) These are not able to prevent physical nerve root compression and are inappropriate for massive disc prolapses causing motor weakness or numbness in the leg.

Currently there is no evidence comparing steroid injections given via the nerve foramen to any other form of treatment i.e. surgical microdiscectomy. Neither has a robust economic analysis been performed for this condition and these treatment paradigms.

Previous studies of microdiscectomy for sciatica
Recent data from Peul et al (3, 6) suggests that surgical microdiscectomy may effectively relieve sciatica in 90% of patients with acute sciatica. This is comparable to favourable outcomes from conservative management of the condition at 12 months follow up. This above finding would suggest that there is a period of spontaneous resolution for this condition within the first 12 months of symptom onset, though surgical intervention could lead to quicker recovery. Treatment may be needed for patients in the acute phase of their condition and to prevent their symptoms from becoming chronic and resistant to treatment/intervention.
Surgery to remove a prolapsed lumbar intervertebral disc (PID) is regarded as the gold-standard treatment for acute sciatica. Adverse events are reported in up to 3% of operations and include the same spectrum of complications as SNRI but also death, paraplegia, sexual/bladder dysfunction and spinal fluid leak. Approximately 6% of operated herniated discs can recur and require re-operation (14). The long-term deleterious effects of this operation upon the patient are unknown. Specialist centres in the UK can carry out more than 500 primary microdiscectomy operations per year for this condition. The average length of stay for this procedure is two nights in hospital.

The advantages of microdiscectomy are:
a) It has the highest reported success rate, working in 9 out of 10 patients.

Disadvantages are:
a) It is expensive, requiring hospital admission.
b) There are resource implications given that the skill level required to perform the procedure is high, requiring a consultant spinal surgeon (orthopaedic or neurosurgical surgeon) or their equivalent.
c) It carries the highest level of morbidity/risk of all treatments.
d) The long term consequences of surgical microdiscectomy are largely unknown.

2.3 Objectives

NERVES is a two-arm, multi-centre, phase III, randomised trial comparing transforaminal epidural steroid injection to surgical microdiscectomy for acute sciatica. An internal pilot will be completed with two trial sites as part of an initial feasibility study.

Primary objective:

To compare the clinical effectiveness of Transforaminal Epidural Steroid Injection (TFESI) for acute sciatica secondary to prolapsed intervertebral disc (PID) and surgical microdiscectomy.

Secondary objectives:

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

Further details of outcome measures are described in section 4.

2.4 Potential Risks and Benefits

The recruiting clinician will discuss the potential risks and benefits with patients prior to trial entry and they will be outlined in the participant information sheet.

2.4.1 Potential Risks

Both methods assessed in this trial are used routinely at participating sites and the risks are well documented. The main risk is that patients may be allocated to a treatment that on final analysis is found to be less effective than the other. There is currently clinical equipoise among the treatments being tested and both methods assessed in this trial are used routinely at participating sites. TFESI and surgical microdiscectomy have associated risks common to the treatment types detailed in Section 10; however the incidence of these is low.

2.4.2 Known Potential Benefits

There are no known benefits specific to patients taking part in the NERVES trial. Patients recruited into NERVES will receive standard NHS care during the conduct of the trial and will receive one of two treatments, both of which are standard practice. The potential benefit of each intervention is the reduction in pain as all patients entered into the trial will have had non-trivial pain for more than 6 weeks and up to a maximum of 12 months.

3 SELECTION OF CENTRES/CLINICIANS

The trial will generally be run in NHS out-patient neurosurgical, pain and orthopaedic clinics. Patients will be recruited from units receiving patients from pooled tertiary referrals from GPs, allied health professionals and non-spinal consultants.

Participating centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the CTRC. Training meetings will cover the requirements outlined in CTRC SOPs TM017 and TM018.

3.1 Centre/Clinician Inclusion Criteria

a. TFESI performed according to protocol requirements (i.e., specified pharmaceutical agents available from pharmacy via local routine prescription routes)
b. Able to provide both treatments within 12 weeks of randomisation
c. Principal Investigator can be either a representative of neurosurgery or pain management (N.B. both specialties should be represented within the local research team)
d. Clinical equipoise
e. Local R&D approval
f. Completion and return of 'Delegation of Authority and Signature Log' to CTRC
g. Completion and return of Site Suitability Assessment to CTRC
h. Signed contract between site and sponsor
i. Receipt of evidence of adherence to (a – g) by CTRC
j. Complete progression through the Green Light Check List

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above

4 TRIAL DESIGN

4.1 Primary Endpoint

a. Oswestry Disability Questionnaire (ODQ) at 18 weeks after randomisation (approximately 3 months post treatment)

4.2 Secondary Endpoint(s)

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

4.3 Internal Pilot

The trial will include a 6 month internal pilot involving two lead centres (Liverpool [Walton Centre] and Manchester [Salford Royal]). These centres have been identified to cover recruitment of participants within specialty and mixed care settings. The expected recruitment in the two lead centres over 6 months is 30 participants. See section 9.5.1 for details.

Sites other than those involved in the internal pilot will continue to progress though the CTRC green light checklist with site initiation dates arranged or completed by the end of the internal pilot stage.

5 STUDY POPULATION

5.1 Inclusion Criteria

Patients meeting the following criteria will be eligible for inclusion in the trial:

a. Diagnosed lower extremity radiculopathy (sciatica)
b. Sciatica secondary to prolapsed intervertebral disc (PID) proven by MRI
c. Duration of symptoms between 6 weeks and 12 months*
d. Leg pain non-responsive to conservative, non-invasive management
e. Age 16 – 65 years
f. Patient has attempted at least one form of conservative (non-operative) treatment** but this has not provided adequate relief of patient's pain/symptoms
g. Patient has provided written, informed consent

If symptoms are episodic then 'duration of symptoms' refers to the initial incidence of severe symptoms (i.e., the disc prolapse). It **does not** refer only to the most recent episode.
** Including but not limited to; medication, physiotherapy, modification of daily activities

5.2 Exclusion Criteria

Patients meeting the following criteria will be excluded from the trial:

a. Serious neurological deficit (e.g. foot-drop/possible cauda-equina compression)
b. Previous spinal surgery at the same intervertebral disc (level)
c. Sciatica presentation for longer than 12 months (see 5.1c. above for more information)
d. Age < 16
e. Age > 65
f. Patient has not attempted any form of conservative treatment
g. Any patient who has a contraindication for surgery and/or injection
h. Patient known to be pregnant

Contraindications for both arms of treatment are to be assessed on a case by case basis by the healthcare team as per routine NHS practice and according to local policy.

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection.

5.3.1 Discontinuation of Trial Treatment: Patient does not receive their randomly allocated treatment

If a patient does not receive their randomly allocated treatment for example if their condition changes and the allocated treatment is no longer appropriate or the patient decides not to have the allocated treatment for any reason, the patient should be asked to allow continuation of scheduled follow-ups. They should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.

Follow-up of these patients will be continued through the trial by Research Nurses, the lead investigator at each centre and, where these are unsuccessful, through the trial coordinating centre, unless the participant explicitly also withdraws consent for follow-up.

5.3.2 Withdrawal from trial

Patients are free to withdraw consent up to the point that final data analysis starts. A withdrawal CRF should be completed that documents the level of withdrawal. The study team will keep their randomisation details and withdrawal form as evidence that original consent to take part in the study was provided and then subsequently withdrawn. All other information collected about the patient will be deleted/destroyed and not used in the study analysis.

5.3.3 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. If this is not possible, the original centre should make every effort to continue with follow up as per protocol.

A copy of the patient CRFs should be provided to the new participating site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The CTRC should be notified in writing of patient transfers.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

All patients who attend a participating trial centre following referral for sciatica secondary to PID (previously proven on MRI) will be prospectively screened for trial eligibility. Trial information will be provided to patients at, or prior to, the clinic appointment. Potentially eligible patients (i.e. those that meet the eligibility criteria listed in section 5) will be invited to participate in the trial. At the clinic appointment the patient will be allowed time to discuss the trial, ask questions and decide whether to consent to take part in the trial. Due to the pragmatic nature of the trial, it is expected that patients will provide written, informed consent at the initial visit without requiring further time to consider participation (see section 11.3 for consent procedures). Patients requiring additional time to consider consent should be managed on a case by case basis at a site level as an additional visit may be required.

A screening log will be maintained at each trial centre recording all individuals screened for the trial and the eventual outcome. Reasons for non-recruitment will be documented (e.g. not eligible, declined consent etc.) and the information will be used for monitoring purposes. Patients will be asked if they would like to provide a reason for non-consent although they are not obliged to provide one. Reasons for non-participation that relate to patient preference should be recorded with the undesired treatment listed when possible.

6.2 Baseline and Eligibility

After obtaining written informed consent the baseline Case Report Form (CRF) should be completed to assess and confirm eligibility. The baseline CRF includes a medical and neurosurgical history based on source data in the patient notes and eligibility should be confirmed by an appropriately qualified doctor. This duty should be delegated on the Delegation of Authority and Signature log. The details of recruitment into the NERVES trial should be recorded appropriately in the patient notes i.e., details of eligibility confirmation (when and by whom), consent and entry into the trial.

Participants will also be asked to complete a questionnaire booklet (incorporating ODQ, Roland-Morris, COMI, numerical rating scores for leg and back pain, and a health economic assessment) with support from a health professional if needed. The participant completed questionnaires must be completed prior to randomisation but after provision of consent. The ODQ collects primary outcome data for the trial so it is important that this booklet is completed accurately and hence it should be checked by sites and assistance provided in completing it if required.

6.3 Randomisation

Patients should not be randomised until:

a) Fully informed written consent has been obtained from the patient
b) The baseline CRF has been accurately completed
c) Full eligibility has been confirmed by a doctor

Participants will be randomised using an online web randomisation system. Designated members of the trial team at site, as detailed on the Delegation of Authority and Signature log, will be given training to use the online system and then will be provided with unique log in details. Data captured on the baseline Case Report Form will be entered into the online system to confirm eligibility of the participant and provide information needed for treatment allocation. Randomisation should occur at the initial clinic appointment if possible. Any delays to confirmation of treatment allocation incurred as a result of trial participation should be agreed with the patient prior to enrolment and documented appropriately.

The online system will allocate a unique randomisation number to the participant together with their treatment allocation. The CTRC will receive an email notification that randomisation has taken place.

Randomisation:
Web access: https://ctrc.liv.ac.uk/Randomisation/Nerves

If there are any problems with the randomisation systems, please contact the CTRC helpdesk on: **0845 68 00 951**

Or via email on: **helpdesk@mcrnCTRC.org.uk** or **nerves@liverpool.ac.uk**

(Note that the CTRC is open from 0900 – 1700, Monday – Friday, excluding public holidays)

7 TRIAL TREATMENTS

7.1 Ionising Radiation Medical Exposure Regulations 2000

Participants in the study will receive a small exposure to ionizing radiation in both arms of the trial. This is required to provide imaging for verification of the treatment level for both microdiscectomy and TFESI. The ionizing radiation exposure is required as part of the normal care pathway and the same exposure would be necessary outside of this clinical trial context. There is no additional ionizing radiation exposure to participants as a result of trial participation.

7.2 Arm A – Transforaminal Epidural Steroid Injection (TFESI)

Standard nerve root blockade will be completed as per local policy/technique using the lateral, foraminal portal of entry so there is no requirement to delegate this as a trial-specific duty. All fluoroscopically guided techniques (e.g., CT or X-ray screening) will be permitted to specify the correct level. Treating specialists will include pain specialists, radiologists, anaesthetists, surgeons (or other appropriately qualified medical professionals) as long as radiological level confirmation is incorporated into the procedure.

NERVES is a pragmatic trial and as such the agents used are expected to be obtained and prescribed via normal NHS routes. To minimise variability across the participating sites it is expected that the following injection regimen will be followed where possible:

- Injectate:
    - Steroid
      20 - 60 mg triamcinolone acetonide e.g., Kenalog
    - Local anaesthetic
      0.25% levobupivacaine hydrochloride (2ml) e.g., Chirocaine

As NERVES is a CTIMP, information regarding the pharmaceutical products used must be provided to the MHRA. The following active ingredients were notified to the MHRA and therefore are also accepted for use in TFESI if appropriate:

Steroid:

- Dexamethasone
- Depo-Medrone

Local anaesthetic:

- Bupivacaine hydrochloride
- Lidocaine hydrochloride

N.B. Relevant SPCs for pharmaceutical products are available on the eMC website (https://www.medicines.org.uk/emc/)

For the purpose of patient safety it is expected that sites will ensure the following maximum doses are not exceeded:

Injectate:	Maximum Dose:
Triamcinolone acetonide e.g. Kenalog	80 mg
Levobupivacaine hydrochloride e.g. Chirocaine	10 mg
Dexamethasone	20 mg
Methylprednisolone acetate e.g. Depo-Medrone	80 mg
Bupivacaine hydrochloride	10 mg
Lidocaine hydrochloride	40 mg

Please note, where the maximum dose is exceeded a data query form will be produced at CTRC and sent to site requesting justification.

Information on exact dosage and agents used, the level of injection and whether the block was ganglionic (at the level of the index disc) or preganglionic (the level below the disc) will be collected.

All patients randomised to Arm A will receive at least one therapeutic injection. As per local policy patients may receive another injection if there is a favourable but partial response that could be boosted by further injections. Information about any further injections will be collected.

Treatment will be given within 6 weeks of randomisation where possible. Treatment must occur within 12 weeks of randomisation to ensure valid collection of primary outcome data at the 18 week follow up.

The steroid/anaesthetic combination used in the TFESI will be distributed from pharmacy via routine processes and so specific trial labelling is not required as per MHRA exemption Regulation 46. TFESI is off-label use of steroid, but is commonly accepted practice within the NHS and in the further medical field.

7.3 Arm B – Surgical Microdiscectomy

Standard microdiscectomy will be performed as per local treatment protocols so there is no requirement to delegate this as a trial-specific duty.

Sites will identify the correct side (left or right) and level prior to treatment with level localisation advised as per local treatment protocols. Information on site and level will be collected.

Treatment specialists would be either an Orthopaedic or Neurosurgical consultant/consultant equivalent (associate specialist) or a specialist trainee directly supervised by a consultant.

Treatment will be given within 6 weeks of randomisation where possible. Treatment must occur within 12 weeks of randomisation to ensure valid collection of primary outcome data at the 18 week follow up.

7.4 Cross Over Between Trial Treatments/Additional Treatments

The NERVES trial protocol will only allocate **initial treatment** for sciatica, either TFESI or microdiscectomy. During the course of follow up participants may require further intervention for sciatica as per routine NHS practice. Further clinical intervention is permitted for trial participants without the patient having to withdraw from the trial.

If a patient receives additional treatment information on the type of intervention (e.g., TFESI or surgery), the details of the treatment received and the reason will be collected and the patient should stay in the trial.

Trial participants are able to crossover prior to receiving their initial treatment allocation **without withdrawing from the trial** e.g., if they become unsuitable for the treatment they are initially randomised to. This should be recorded on the treatment CRF with the reason for crossover indicated.

7.5 Accountability and Assessment of Compliance for Study Treatment/s

7.5.1 Accountability

NERVES is a pragmatic rather than exploratory trial and the intention is to measure outcomes associated with treatments that reflect real life clinical practice in the NHS.
There are no formal accountability measures required for the trial, as treatments will be prescribed according to the local medical practices and dispensed by hospital and community pharmacies as they would be normally in clinical practice.

7.5.2 Assessment of Compliance with the Study Intervention

The CTRC will monitor compliance with the randomised study intervention 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. As NERVES is a pragmatic trial the interventions are expected to reflect local NHS policy and so variation within the interventions is expected.

7.6 Concomitant Medications/Treatments

NERVES is an unblinded trial therefore decisions about concomitant medications/treatments will depend on the local medical plan and clinical management. Details of concomitant medication will be collected on a dedicated CRF. In the event of a Serious Adverse Event concomitant medication information will be captured on an SAE CRF.

7.7 Co-enrolment Guidelines

To avoid potentially confounding issues, patients should ideally not be recruited into other trials. Where recruitment into another trial is considered to be appropriate and unlikely to have any detrimental effect on the NERVES trial this must first be discussed with the coordinating centre who will contact the Chief Investigator.

8 ASSESSMENTS AND PROCEDURES

Data will be collected using paper CRFs and participant completed questionnaires. All CRFs (with the exception of participant completed questionnaires) should be completed by personnel named on the delegation log as authorised to do so. Participant eligibility should be confirmed by an appropriately trained and medically qualified member of the research team who has been delegated that duty. There is no requirement for authorisation of the person who administers the randomised treatment because both treatments are routine NHS practice. CRFs and completed questionnaires should be photocopied for maintenance at site and originals should be returned to the CTRC within 3 weeks of the visit date unless specified otherwise (see Table 1 in Section 8.1 for CRF Return Schedule).

Where questionnaires are sent directly to the participant they will be sent by the investigating site research team. Questionnaires sent to the participant must be supplied with a pre-addressed, pre-paid envelope and will be returned to the CTRC by the patient using the envelope provided. The research team should ensure that questionnaires are pre-populated with the required information (randomisation number, timepoint details etc.) before sending to the patient.

Each site will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the coordinating centre. They will also keep copies of all completed CRFs and participant completed questionnaires for the trial. Correct completion of these documents is very important and every effort should be made to minimise missing data and incorrect completion. Completion of CRFs is described further in Section 13.3.

Once written informed consent has been obtained from the patient (see Section 11.3 for more information) the research team will collect baseline characteristics using the baseline CRF and the patient will be randomised and followed up in the trial. For screening and randomisation procedures refer to Section 6. For details of procedures associated with trial treatments refer to Section 7. For a summary of trial assessments see Table 3 in Section 8.1.

Participant details including name, initials, date of birth, postcode, NHS number and randomisation number will be reported on the consent form, separate to clinical data.

8.1 Schedule for Follow-up

All follow up visits will be scheduled from the ***date of randomisation*.**

Each participant will be followed up for 54 weeks following randomisation. During this time participants will attend scheduled follow up visits. Any additional procedures provided to the participant and completed at the trial site during this period will be documented as described in Section 7.4

Prior to intervention, patients will attend an appointment at the trial site as per NHS referral. If consent is provided the participant is randomised and should receive treatment as per local NHS policy.

Normal clinical practice would normally include a 3 month post-treatment follow up. Therefore patients will be followed up at approximately 18 weeks post-randomisation to align with routine clinical practice, and then at 30, 42, and 54 weeks. To maintain feasibility the 18, 30 and 42 week visits can be conducted 2 weeks either side of the specified number of weeks. The 54 week visit has an acceptable window of 54-62 weeks post-randomisation. Patients may be seen at other times as clinically indicated. Additional visits outside of the trial protocol will be recorded.

After randomisation, scheduled treatment and follow-up stages are as follows:

Treatment visit: Treatment details are recorded on form 3; treatment. The patient will be presented with Resource Use Questionnaire Booklet 2 and asked to fill it in prior to their treatment. The site will be asked to co-ordinate provision of Resource Use Questionnaire Booklet 2 to the patients in pre-op. Contraindications for treatment (such as pregnancy) will be assessed by sites as per NHS policy and therefore no additional trial-specific assessments will be conducted at this visit.

Where a participant chooses to not proceed with their allocated treatment prior to treatment being given the participant will still be expected to continue with trial follow-up and attend the follow-up visits. If a participant does not wish to continue in the trial, a Withdrawal CRF will be completed to capture the date and reason for trial withdrawal as detailed in section 5.3.2.

Week 18 and 54 (visits)

- Face to face follow-up visit (post-operative for W18)
- Site will be responsible for organising the follow up within the visit window (specified in the email when the participant is randomised).
- Visits should be arranged for within first 2 weeks of visit window where possible; this then gives the site time within visit window to take action if participant does not attend their appointment.
- Participant will be expected to undergo a physical examination and complete the assessments as listed in Table 3 (includes completion of Patient Questionnaire Booklet 1)
- Site returns Form 4: Follow-up Visits and any other appropriate updated CRFs as applicable (e.g., Form 5: Concomitant Medication, Form 6: Related Adverse Events)
- Pregnancy should be assessed; if a patient reports pregnancy the pregnancy CRF should be completed and returned to the CTRC within 24 hours.
- The week 54 visit may fall out of routine follow up care; patients will be able to claim reasonable expenses for attending this appointment (see Section 15).

Participants not attending Visits (Weeks 18 and 54)
It is important that the patient attends the Week 18 visit as this is when the primary outcome data for the trial is collected. The participant should be contacted as per trust policy to urge them to attend.

If these attempts fail, the trial site should email CTRC to seek approval to post out the Patient Questionnaire Booklet 1, explaining circumstances. CTRC will indicate whether the Patient Questionnaire Booklet 1 can be posted to the participant if the participant does not attend their visit and all attempts of contact have failed.

Visits should be arranged initially for the first two weeks of the visit window as this gives time for the questionnaire booklet to be sent out by post and completed by participant within visit window in cases of non-attendance. The questionnaire booklet should be accompanied by the standard covering letter and a pre-paid envelope to enable the patient to return the booklet directly to CTRC.

If a visit does not take place, the site should also telephone the patient to try and retrieve as much Form 4: Follow-up Visits information as possible over the telephone (such as adverse event information, date returning to work) and record the information obtained in the patients notes as source data. This telephone call should be carried out by the person who was due to conduct the visit. Information obtained and recorded within source data should then be transcribed onto Form 4 and returned to CTRC. If information is unable to be obtained by

telephone, Form 4 should still be returned to CTRC notifying a non-attendance (Did Not Attend - DNA).

For the Week 18 visit **only**, a telephone call may be used to collect primary outcome data (**Part 1** of Patient Questionnaire Booklet 1 (ODQ)) in exceptional circumstances, with agreement from the CTRC. A telephone call must only be used to collect this data if all attempts to urge the patient to attend their Week 18 visit have failed, and the patient has not returned the Patient Questionnaire Booklet 1. Trial sites should contact the CTRC in this scenario to ensure all options for patient attendance at the Week 18 visit have been exhausted and to receive a script for the telephone call.

Week 30 and 42 (postal)

- The investigating site research team will post Patient Questionnaire Booklet 1 and a standard covering letter to the participant at the start of the W30/42 window, with a pre-paid envelope for the participant to post back the booklet to the CTRC.
- Form 4: Follow-up Visits should be completed by trial site and returned to CTRC to confirm the date that the questionnaire booklet has been posted out.
- Where a response has not been received (notified by the CTRC) the site research nurse will telephone the participant to prompt completion and return of the questionnaire booklet, and offer any help required to ensure the questionnaire booklet is completed accurately.

The following tables have been provided to summarise the information provided in Section 8.1. Table 1 and 2 summarise the expected CRF completion and return schedules. Table 3 details the schedule of assessments to be undertaken for the randomised participants. It is expected that research sites will make every effort to adhere to these schedules.

Table 1: Case Report Form Completion Schedule

Visit	Visit Type	Compulsory CRFs	Additional CRFs (complete only if applicable)
Baseline	Face to face	**1.** Screening Log[1] **2.** Informed Consent **3.** Form 1: Baseline and Eligibility **4.** Patient Questionnaire (Booklet 1)	**1.** Form 2: Randomisation[2] **2.** Form 5: Concomitant Medications **3.** Form 14: Pregnancy
Treatment	Face to face	**1.** Form 3: Treatment Form **2.** Resource Use Questionnaire (Booklet 2)	
Week 18	Face to face	**1.** Form 4: Follow Up Visits **2.** Patient Questionnaire (Booklet 1)	**1.** Form 5: Concomitant Medications **2.** Form 6: Related Adverse Events **3.** Form 7: Serious Related Adverse Event Report Form[3] **4.** Form 8: Additional Treatment **5.** Form 14: Pregnancy
Week 30	*Postal*	**1.** Form 4: Follow Up Visits[4] ***2.*** *Patient Questionnaire (Booklet 1) - site to post to patient*	
Week 42	*Postal*	**1.** Form 4: Follow Up Visits[4] ***2.*** *Patient Questionnaire (Booklet 1) - site to post to patient*	
Week 54	Face to face	**1.** Form 4: Follow Up Visits **2.** Patient Questionnaire (Booklet 1) **3.** Form 9: PI Authorisation Form[5]	**1.** Form 5: Concomitant Medications **2.** Form 6: Related Adverse Events **3.** Form 7: Serious Related Adverse Event Report Form[3] **4.** Form 8: Additional Treatment **5.** Form 14: Pregnancy
Unscheduled	Face to face	**1.** Form 4: Follow Up Visits	**1.** Form 5: Concomitant Medications (applicable if related to any AE) **2.** Form 6: Related Adverse Events **3.** Form 7: Serious Related Adverse Event Report Form[3] **4.** Form 8: Additional Treatment **5.** Form 14: Pregnancy

[1] Screening Log to be completed for **all** potentially eligible patients attending clinic following GP referral.
[2] Form 2 is only required in case of failure of the web-based randomisation system.
[3] Form 7 is only to be completed if a related adverse event meets the criteria of **serious.** If completed it must be returned by fax to the CTRC **within 24 hours**.
[4] Form 4 is to be completed at postal visits by research staff at site to document postage of Patient Questionnaire Booklet 1
[5] PI Authorisation form is to be used as the end of the follow up period to confirm that all data are complete
[6] Forms 10-14 are non-routine CRFs but may also be applicable at any timepoint. These should be reviewed on a case by case basis

Table 2: Case Report Form Return Schedule

Form #	Name of CRF	Return Schedule
N/A	Screening Log	Month end (fax)
N/A	Informed Consent	7 days (fax)
1	Baseline and Eligibility	7 days
2	Randomisation	21 days
3	Treatment Form	21 days
4	Follow up visits	21 days
5	Concomitant Medication	21 days*
6	Related Adverse Events	7 days (unless SAE)**)
7	Serious Related Adverse Event Report form	24 hours (fax)
8	Additional Treatment	21 days
9	PI Authorisation Form	21 days
10	Death Form	7 days (unless SAE**)
11	Withdrawal from Follow Up	14 days
12	Patient Transfer	7 days
13	Participant Data Withdrawal	14 days
14	Pregnancy	24 hours (fax)
N/A	Patient Questionnaire (Booklet 1)	21 days / Patient returned
N/A	Resource Use Questionnaire (Booklet 2)	21 days

* A **copy** of Concomitant Medication and Related Adverse Events forms should be returned following each update until original is fully completed/final visit
** If any adverse event (recorded on Form 6) or death (recorded on Form 10) meets the criteria of a Serious Adverse Event then the relevant forms should be faxed to the CTRC within 24 hours along with a Serious Related Adverse Event form (Form 7) and should contain the minimum information required for reporting (see Section 10 for further information)

Every effort should be made to ensure correct completion of all CRFs and patient questionnaire booklets. Where possible, patient questionnaires should be checked by research staff before the end of the patient visit so that any mistakes or omissions can be rectified.

Table 3: Trial Assessments

Procedures	Screening / Baseline (T = 0)	Follow-Up Schedule: Intervention T=6 weeks [2]	Time Point T = 18 weeks	Timepoint T = 30 weeks[3]	Timepoint T = 42 weeks[3]	Timepoint T = 54 weeks	Unscheduled visits[5]
Signed Consent Form	X[1]						
Assessment and Confirmation of Eligibility Criteria	X[1]						
Review of Medical History	X[1]						
Review of Concomitant Medications	X[1]	X	X			X	
Oswestry Disability Questionnaire	X[1]		X	X[3]	X[3]	X	
Health Economic Assessment	X[1]	X	X	X[3]	X[3]	X	
EQ-5D-5L	X[1]		X	X[3]	X[3]	X	
Numerical rating score for leg and back pain	X[1]		X	X[3]	X[3]	X	
Modified Roland-Morris outcome score for sciatica	X[1]		X	X[3]	X[3]	X	
Core Outcome Measures Index (COMI)	X[1]		X	X[3]	X[3]	X	
Study Intervention		X					
Pregnancy Assessment	X	X	X			X	X
Physical Examination	X[1]		X			X	
Treatment satisfaction (Likert scale)			X	X	X	X	
Return to work			X			X	
Assessment of Related Adverse Events		X	X			X	X
Assessment of additional interventions given to the participant during the trial period			X			X	X[5]
Telephone follow up of non-responders				(X)[4]	(X)[4]		

(X) – As indicated/appropriate.

[1] Completed prior to randomisation
[2] Treatment is expected to occur within 6 weeks of randomisation and no later than 12
[3] Patient is not required to attend clinic at 30 and 42 weeks; Questionnaire posted to the participant by the trial site and posted back to the CTRC by the patient
[4] Telephone follow up will typically follow one week after initial issue of questionnaire
[5] Additional visits for further treatment (e.g. TFESI or surgery) may occur as part of routine practice

8.2 Procedures for assessing Efficacy

Efficacy of the trial treatments will be measured through the period of the trial using a number of outcome measures:

i. Oswestry Disability Questionnaire (ODQ) at 18 weeks after randomisation (approximately 3 months post treatment)
ii. ODQ at 30, 42 and 54 weeks after randomisation
iii. Numerical rating scores for leg pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation
iv. Numerical rating scores for back pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation
v. Likert Scale to assess patient treatment satisfaction at 18, 30, 42, 54 weeks after randomisation
vi. Modified Roland-Morris outcome score for sciatica at baseline, and at 18, 30, 42 and 54 weeks after randomisation
vii. Core Outcome Measures Index (COMI) at baseline, and at 18, 30, 42 and 54 weeks after randomisation
viii. Work status (return to work and work days lost)
ix. Cost-effectiveness, expressed as the incremental cost per quality-adjusted life-year (QALY) based on the EQ-5D-5L

8.3 Procedures for Assessing Safety

An assessment of adverse events will be undertaken at each study clinic visit post-treatment. These reviews should be carried out by the Principal Investigator or delegated research staff. Adverse event reporting is detailed in Section 10.

8.4 Other Assessments

8.4.1 Quality of Life

Participants will be asked to complete the following patient reported outcome measures at baseline, 18, 30, 42 and 54 weeks after randomisation; these have been incorporated into a single patient questionnaire booklet (Patient Questionnaire Booklet 1):

- Oswestry Disability Questionnaire
- Modified Roland-Morris outcome score for sciatica
- Core Outcome Measures Index (including Likert scale for treatment satisfaction)
- EQ-5D-5L
- Numerical rating score for leg and back pain

Patient Questionnaire Booklet 1 (to be completed at baseline, week 18 and week 54 week follow up) will be provided to the participant at the scheduled clinic visits and completed in clinic. Resource Use Questionnaire Booklet 2 is to be completed at the treatment visit **before** treatment and will be provided to the participant in pre-op.

Completion of these questionnaires is an important part of the trial. Particular emphasis should be given to Part 1 of Patient Questionnaire Booklet 1 (ODQ) because it is used to collect primary outcome data for the trial. It is therefore crucial that research staff at site offer any

necessary support to participants to ensure the questionnaires are completed correctly and returned to CTRC either by site or by the participant in accordance with the schedule for follow-up. It is estimated that the questionnaires will take approximately 15 minutes to complete and participants should be advised of the extended visit time prior to their appointment.

All questionnaires completed at baseline will be completed after consent has been provided and prior to randomisation.

8.4.2 Health Economics

The health economic analysis will adopt the perspective of the National Health Service (NHS) and Personal Social Services (PSS) and additionally consider indirect costs such as time off work (secondary analysis).

Resource use will be based on entries made in patient questionnaire booklets, and Hospital Episode Statistics data sourced from NHS Digital for patients recruited in England.

- Data on Hospital Episode Statistics (HES) will be collected centrally from NHS Digital who operate under a General Data Protection Regulation (GDPR) framework, which ensures that the data will be:
  - Consented in a way that obtaining it will not be a precondition of signing up for the trial
  - Consented in a way that patients will be informed unambiguously via the patient information sheet, that their personal data will be sent to NHS Digital in order for NHS Digital to supply patient HES data, and that their anonymised HES data will be sent by NHS Digital to Bangor University Centre for Health Economics and Medicines Evaluation (CHEME) for analysis
  - Granular inasmuch as consenting to processing of patient HES data is a separate statement on the consent form. Patients will be informed in the information sheet of CTRC and the third party (CHEME) involvement who will be relying on consent.
  - Subject to records being kept to demonstrate what each patient has consented to, including what they were told, and when and how they consented.
  - Subject to consent being also easy to withdraw and patients being told in their consent forms they have the right to withdraw their consent at any time, and how to do this.

Data collected from NHS Digital will include Hospital Episode Statistics on outpatient, inpatient and A&E attendances by each patient from the beginning of the financial year immediately prior to the first patient being enrolled, to (and include) the end of the financial year immediately prior to, or following, the final follow-up of the last patient.

Patient information (postcode, date of birth, NHS number and trial number) will be collected by CTRC to generate a secure database which will enable them to request HES data from NHS Digital. The database will only be accessible by authorised personnel working on the trial or shared with authorised personnel working at NHS Digital. At the time of the data request, the database will be provided to authorised personnel at NHS Digital via a secure link and the HES data with the trial number will be sent to CTRC by NHS Digital also via a secure link. NHS Digital will be asked to remove patient personal identifiers such as NHS number, date of birth, pseudohesid and gender at source. Data received by CTRC will be stored and disposed of in accordance with their Data Sharing Framework Contract (DSFC) with NHS Digital.

Anonymised and encrypted HES data will be transferred to CHEME via a secure link and stored at Bangor University in accordance with their NHS Digital DSFC. The only identifier present in the dataset will be the trial randomisation identifier and CHEME will not have any access to keys linking this to patient personal data. Access will be restricted only to health economists working on the trial, and data will only be accessed by username and password. Once the analysis has been completed the HES data will be securely disposed in accordance with the CHEME NHS Digital DSFC.

Requests for anonymised extracts will be made according to standardised procedures 6 months after the final follow-up of the last patient randomised. Patients' use of primary care services, personal social services, non-scheduled clinic attendance, out-of-pocket expenditures and indirect costs will be collected at baseline and at 18, 30, 42, 54 weeks post-randomisation by administering a specifically designed resource use questionnaire (incorporated into patient questionnaire booklets). Completion of the resource use questions should take approximately 10 minutes. Unit cost data will be obtained from standard sources (NHS reference costs and PSSRU Costs of Health and Social Care).

The health outcome measure will be the quality-adjusted life-year (QALY), estimated by administering the EQ-5D-5L at each follow-up point. The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule, applying the UK tariffs (as they become available for the EQ-5D-5L) and corrected for baseline utility score.

8.4.3 Pregnancy

Pregnancy should be assessed at the following timepoints:

- Baseline – assessment of pregnancy forms part of the assessment of eligibility and should be recorded on the Baseline and Eligibility CRF; patients who are pregnant at baseline are ineligible for the trial
- Treatment – assessment of pregnancy should be undertaken as local NHS policy prior to proceeding with treatment; patients who are pregnant at the scheduled time of treatment are contraindicated for treatment
- 18 week follow up – patients will be asked to self-report pregnancy which will be recorded in the Pregnancy CRF
- 54 week follow up – patients will be asked to self-report pregnancy which will be recorded in the Pregnancy CRF

8.5 Substudies

There are no substudies associated with this trial. An internal pilot will be conducted as part of trial feasibility; details are provided in section 9.4.1.

8.6 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the research team at each centre. If the lead investigator at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this latter clinician. This information will be included on the patient information sheet. Wherever possible, information on the reason for loss to follow-up will be recorded.

Attempts to follow up the patient should continue until the end of the trial and patients should not be withdrawn unless the patient specifically requests this.

8.7 Trial Closure

The end of the trial is defined to be the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (ISDMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed with the TSC before being sent to the IDSMC for comment and approval.

9.2 Method of Randomisation

Randomisation will be stratified by study centre. Randomisation schedules will be generated for each stratum using block randomisation, with random variable block length.

9.3 Outcome Measures

See Section 4 for primary and secondary outcome measures.

9.4 Sample Size

The primary outcome measure of Oswestry Disability Questionnaire (ODQ) has over thirty years of validation and is supported by OMERACT for low back pain research. Deyo et al (15) has recommended the use of ODQ as part of the core outcome measures for low back research. This outcome measure is supported by OMERACT in low back research. The scale ranges from 100 (extreme disability) to zero (extreme ability). A change of 10 points has been widely regarded in the literature as the minimal clinical significance. One study (16) specifically addressing this issue has suggested a range of 10.5 to 15 as clinically important. ODQ has over 30 years of validated, published data pertaining to low-back pathology and radicular symptoms. It has formed the basis for previous HTA trials exploring sciatica and will allow useful comparisons to be made to previous data.

In order to detect a difference between the two groups of 10 points on the ODQ at a 5% significance level with 90% power, a total of 172 participants are required. This assumes a standard deviation of 20 points based on a similar population in previous published trials (9, 15-18). The previous large and well-carried out WEST study based in the UK, suggested baseline ODQ SD between 16-18 (9). We have collected baseline ODQ data on 11 potentially eligible patients from the fast track sciatica clinic at the Walton Centre and this generated a standard deviation of 14.4, well under the assumed value. We will aim to recruit a target of 200 patients to allow for a 10% rate of missing outcome data. Of the 7 centres involved, allowing for one to have difficulties opening, this would then require recruitment of 30 patients in total from each participating centre and 50 patients from the lead centre. Potential recruitment populations could be as high as 500 patients per centre per year (based on HES data from numbers of lumbar microdiscectomies performed). Even assuming 50% ineligibility and 40% consent, this low rate of 30 patients per centre per year is realistic. The standard deviation used in this calculation will be checked after approximately 30 patients have been randomised and provided primary outcome data. This blinded internal pilot will not have any significant impact on the final analysis (19).

9.4.1 Internal Pilot Study

An internal pilot study is included in the trial design. The study will target two centres to open first. These centres have been identified to cover recruitment of participants within specialty and mixed care settings. Liverpool [Walton Centre] and Manchester [Salford Royal] will be used for the internal pilot study.

The aim of the internal pilot study is to assess the feasibility of recruitment, and the rates of potential cross-over due to patient preference or treatment failure. Details of the analysis of the internal pilot study are given in section 9.5.1.

9.4.2 Revised sample size

The original sample size calculation did not assume any correlation between baseline and follow-up ODQ scores, as no data was available to estimate this. Based on a blinded analysis of the correlation between baseline and follow-up ODQ scores in the first 47 trial participants to have outcome data available, we can estimate this correlation as 0.49.

Using this estimate, our revised sample size to achieve 90% power is 66 per group. Allowing for 10% loss to follow-up gives a revised target of 74 per group (148 total).

9.5 Interim Monitoring and Analyses

9.5.1 Internal Pilot

After the internal pilot, if all of the following criteria are met, then the trial will progress to the main phase.

(1) At least 30 patients have been recruited at the end of the internal pilot study.
If fewer than 30 patients are recruited, then ways to improve recruitment will be considered, e.g. increasing number of centres, improving consent process to increase patient understanding and willingness to be randomised, widening eligibility based on new evidence.

(2) The consent rate is 40% or more.
If the consent rate is less than 40%, information collected on the reasons for non-consent will be considered to identify any aspects amenable to change. If declining consent is predominantly due to patients favouring one treatment over the other, based on full understanding, then the decision may be made to abandon plans for the full trial.

(3) Fewer than 10% of patients are unhappy with their allocation, and receive the alternative treatment instead.
If more than 20% of patients are unhappy with their allocation, and receive the alternative treatment instead, consideration will be given to not pursuing the main trial. If the number is between 10% and 20%, the consent process at each centre will be explored to ensure that patients have full understanding.

(4) Fewer than 50% of patients in the injection group proceed to surgery.
If more than 50% proceed to surgery, given that this is a pragmatic trial and that meaningful data may still be derived from the results, the TSC/IDSMC will evaluate the reasons behind

crossover and consider stopping the trial if there is a genuine difference in the two treatment efficacies.

Any plans to revise the trial based on these analyses will be submitted to the IDSMC and TSC prior to discussions with the trial funder.

9.5.2 Main trial

The IDSMC are expected to meet 6 monthly, or at least annually, to review the accumulated data on recruitment, safety, effectiveness and trial conduct, in conjunction with external data, and will advise the TSC on whether the data justifies continuing recruitment of patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee as to the continuation of the trial.

9.6 Analysis Plan

The primary outcome (ODQ score at 18 weeks post-randomisation) will be compared between groups using a linear regression model, adjusted for the stratification variable centre, baseline ODQ score, and possibly other (specified in advance) variables considered to be potential confounders. Analysis of secondary outcomes will use similar methods, with logistic regression analyses used where appropriate. The intention to treat principle will be applied as far as is practically possible. The analysis set for the primary outcome will include all participants with an ODQ score at 18 weeks. Reasons for missing primary outcome data will be assessed, blind to treatment allocation, as to whether they are informative of likely outcome. Participants with non-informative reasons for missingness will be excluded from the primary analysis set. Sensitivity analyses will be carried out using multiple imputation to assess the robustness of the analysis to missing primary outcome data.

9.7 Economic Analysis Plan

A full economic analysis plan will be prepared by the trial health economist, and approved as per the statistical analysis plan. Where appropriate, missing resource use or health outcome data will be imputed. Non-parametric bootstrapped 95% confidence intervals will be estimated (10,000 replicates). We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions. Should the data indicate otherwise, we will develop a generalised linear model to deal with problems such as skewness. Total costs will be combined with QALYs to calculate the incremental cost-utility ratio which will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness specified by the National Institute for Health and Care Excellence. A range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis, and multivariate sensitivity analyses will be applied where interaction effects are suspected. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
In the case of the NERVES trial this definition includes any untoward and unintended response to the intervention i.e., the act of injection in the TFESI arm, or surgical microdiscectomy and will be referred to as a Related AE (RAE).

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- In the case of a product with a marketing authorization, in the Summary of Product Characteristics (SPC) for that product.
- In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

In the case of the NERVES trial this definition includes any adverse reaction the nature and severity of which is not consistent with that expected for the act of injection in the TFESI arm or surgical microdiscectomy and will be referred to as a Related Unexpected Serious Adverse Event (RUSAE). See Section 10.4 for more information.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- other important medical events***

*‘Life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when,

based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.3 Relationship to Trial Intervention

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 4.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 4: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. Not reportable for this trial unless the event is death which should be reported on the death form within 7 days
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication/intervention procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication/intervention procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

An AE whose causal relationship to the intervention is assessed by the investigator as "possible", "probable", or "almost certain" is a related Adverse Event or related Adverse Reaction and should be reported to the CTRC (see Figure 1).

For TFESI patients:
When reporting the assignment of causality the investigator should make it clear if the AE is related to the IMP (steroid or local anaesthetic) or to the procedure i.e., the act of injecting.

10.4 Expectedness

It is not a regulatory requirement for reporting physicians to provide their opinion of expectedness; if any adverse events occur the Principal Investigator or delegated other should make an assessment of relatedness to the trial intervention and follow the correct reporting procedure (see section 10.6). The Chief Investigator (or agreed delegate) will undertake the assessment of expectedness.

For TFESI patients:
All events judged to be possibly, probably, or almost certainly related to the steroid and/or anaesthetic used during the TFESI, graded as serious and **unexpected** (see section 10.1 and Table 5 for list of Expected Adverse Events) will be reported as a **Suspected Unexpected Serious Adverse Reaction (SUSAR)** by the CTRC.

For TFESI / microdiscectomy patients:
All events judged to be possibly, probably, or almost certainly related to the microdiscectomy or TFESI *procedure (i.e. the act of injecting),* graded as serious and **unexpected** (see Section 10.1 and Tables 5 and 6 for list of Expected Adverse Events) will be reported as a **related unexpected serious adverse event (RUSAE)** by the CTRC**.**

Based on available safety information for the trial interventions all the events listed in Table 5 and Table 6 are expected within the trial population and will not be subject to expedited reporting to the MHRA or REC. The Chief Investigator will also refer to Reference Safety Information (RSI) for a list of AEs associated specifically with the representative pharmaceutical agents used in the trial (see Section 7.2). The RSI is described within specific sections of Summary of Product Characteristics (SPCs) approved by the MHRA.
N.B. Tables 5 and 6 do not represent an exhaustive list and every related adverse event will be reviewed by the Chief Investigator against available relevant safety information to make an assessment of expectedness.

Table 5: Expected Adverse Events associated with TFESI

A: Events associated with TFESI procedure i.e., act of injecting
Soft tissue infection
Pulmonary Embolism
Deep Vein Thrombosis
Significant post procedural headache (low pressure headache)

Increased sciatic pain post injection Neurological deficit including bladder/bowel issues Anaphylaxis Cauda equina syndrome Foot drop Discitis
B: Events associated with TFESI drugs (IMPs)
Adverse reaction related to administration of steroid (refer to relevant Reference Safety Information) Adverse reaction related to administration of anaesthetic (refer to relevant Reference Safety Information) Anaphylaxis

Table 6: Expected Adverse Events associated with microdiscectomy

A: Events associated with microdiscectomy procedure
CSF leak Significant post procedural headache (low pressure headache) Soft tissue infection Pulmonary Embolism Deep Vein Thrombosis Cauda equina syndrome Foot drop Discitis Reoccurring disc prolapse Anaphylaxis
B: Events associated with general anaesthetic (not required for reporting)
Throat pain/hoarseness Injury to the mouth or teeth from the breathing tube Drowsiness, confusion or restlessness Nausea and/or vomiting Breathing problems Chest infection Anaphylaxis

10.5 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs, RUSAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.6 Reporting Procedures

Any AE with causal relationship to either trial intervention assessed as possible, probable or almost certainly related should be reported to the CTRC using the trial specific adverse event CRF throughout the trial follow up period.

The PI or designated other should grade the event as **'not serious'** or **'serious'**.

- **Events graded as not serious**
  If the event is graded as **not serious,** the adverse event CRF should be returned to the CTRC within 7 days of the clinical research team becoming aware of the event.

- **Events graded as serious**
  If the event is graded as **serious** (see Section 10.1), the investigator should also complete the **Serious Adverse Event CRF and return to the CTRC within 24 hours** of the clinical research team becoming aware of the event and should contain the minimum information required for reporting (see Section 10.7). Any serious adverse event should also be reported as per local reporting procedures.

Do Not Include

- Any AEs whose causal relationship to the trial intervention is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial intervention (microdiscectomy or TFESI).
- Any AEs assessed and considered to be related to the general anaesthetic used
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.
- Additional TFESI or microdiscectomy surgery arising from patient crossover
- Additional TFESI or microdiscectomy surgery arising from treatment failure
- Overdose of any medication without signs or symptoms

Include

- An exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic event/condition.
- A condition (even though it may have been present prior to the start of the trial) detected after the completion of the microdiscectomy or administration of the TFESI).
- Continuous persistent disease or symptoms present at baseline that worsens following the TFESI or microdiscectomy.
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event or as part of routine follow-up).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention.
- Injury or accidents that are not expected but are related to the microdiscectomy or TFESI.

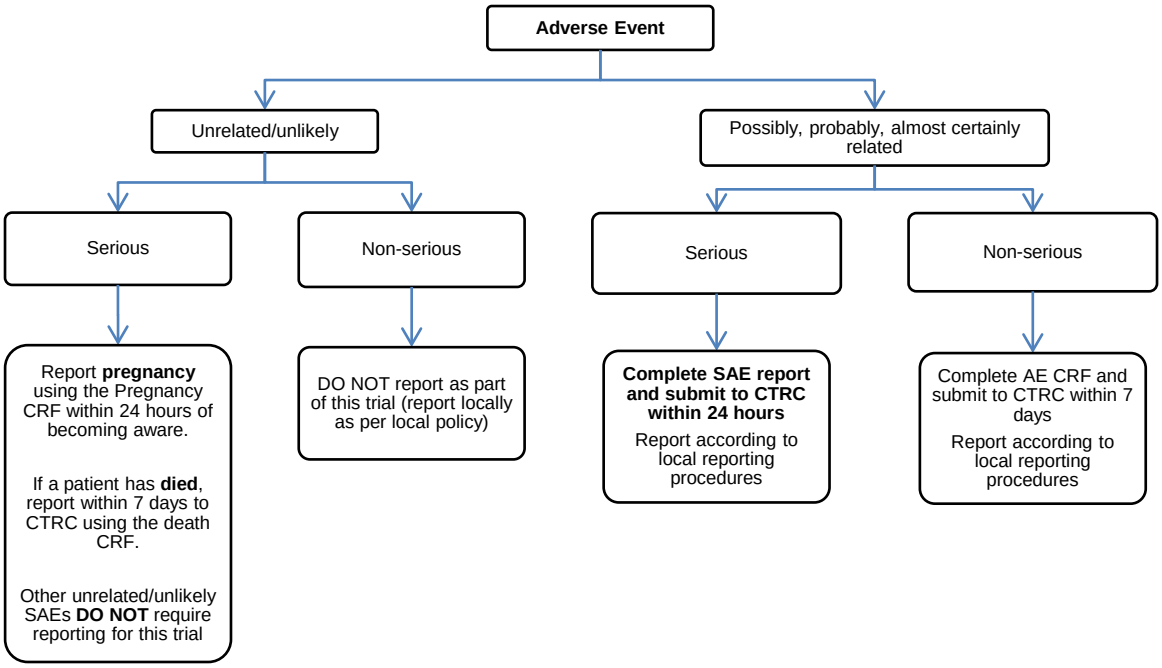
SAEs, SARs/SUSARs and RUSAEs should be reported to the CTRC within 24 hours of the local site becoming aware of the event. The minimum information (see Section 10.7) required for each report should be completed by the investigator. The investigator should sign the causality of the event. Any additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

AEs related to the steroid and/or anaesthetic administered during the TFESI are defined as Adverse Reactions (ARs). If assessed as a Suspected Unexpected Serious Adverse Reaction (SUSAR) by the CI the event will be reported to the MHRA and REC by the CTRC.

AEs related to the microdiscectomy are defined as related Adverse Events (AEs). If assessed as a Related Unexpected Serious Adverse Event (RUSAE) by the CI the event will be reported to the REC by the CTRC.

Figure 1 shows the process that sites should follow when reporting adverse events:

Figure 1: Process of reporting Adverse Events



10.7 Responsibilities – Site Investigator

The Principal Investigator is responsible for reporting all **related AEs** that are observed or reported during the safety reporting period of the study. This is defined from intervention up to and including the Week 54 follow up visit.

Any reportable adverse events classified as Serious must be reported immediately by the investigator to the CTRC on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other reportable adverse events should be reported on the Adverse Event CRF.

Minimum information required for SAE reporting:

- Study identifier
- Study centre
- Participant number
- A description of the event
- Study drug (if applicable)
- Date of onset
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment (i.e., causality)
- Reporter details (i.e., PI details)

i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product or intervention i.e., make an assessment of causality. In the absence of the designated investigator the form should be completed and signed by a delegated alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator to advise that an SAE report has been submitted. Send the SAE form by fax within 24 hours to the CTRC.

iii. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

iv. In the case of an SAE the participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on the original SAE form by ticking the box marked 'follow-up' and completing with additional information before faxing to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

vii. Any additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

10.8 Responsibilities – CTRC

The CTRC is undertaking duties delegated by the trial sponsor, The Walton Centre NHS Foundation Trust, and is responsible for the reporting of RUSAEs, SUSARs and other SARs in the TFESI arm to the regulatory authorities (MHRA and the REC) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

RUSAEs will not be reported to the MHRA but will be reported to the REC within 15 days of first becoming aware.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial and likely to affect the safety of the subjects, such as:
    a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Independent Data Safety Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the CTRC will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SAEs will be reviewed immediately and those that are SUSARs or RUSAEs identified and reported to the MHRA and REC. The causality assessment given by the local investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The PIs at all institutions participating in the trial will be notified of any SUSARs or unexpected SAEs.
Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.8.1 Reporting procedures at the CTRC

The CTRC will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. The CTRC will notify the main REC of all RUSAEs occurring during the study not later than 15 days after being made aware of the event. All investigators will be informed of all SUSARs and RUSAEs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally.

10.8.2 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and AE reporting rates across sites. The CTRC will send Developmental Safety Update Reports (DSURs) containing a list of all SARs to regulatory authorities and a list of all SARs and related SAEs to REC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

10.8.3 Urgent Safety Measures

An urgent safety measure (USM) is a procedure not defined by the protocol, which is put in place prior to authorisation by the MHRA and REC in order to protect clinical trial participants from any immediate hazard to their health and safety.

The sponsor (or agreed delegate) will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the MHRA and REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

If the study is temporarily halted it may not recommence until authorised to do so by the MHRA and REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to MHRA and REC), the sponsor should notify the MHRA and REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

Both of the treatments offered as part of the trial are standard practice. As such there are no major ethical concerns. Where treatment has been considered to be unsuccessful participants will have full access to additional treatment needed as per routine care. Participation in the trial will not prevent access to additional treatments needed.

The specific issues pertaining to this trial are considered to be:

- Requirement for an additional visit
- Patient will be randomised therefore will be unable to choose their own treatment.

Funding is in place to allow reimbursement of financial costs incurred by the trial participant to attend an additional appointment (54 week follow up appointment post-randomisation).

The patient will provide informed consent to participate, ensuring understanding of the randomisation process, data collection and other trial processes.

11.2 Ethical Approval

The trial protocol will receive the favourable opinion of a Research Ethics Committee (REC) prior to initiation at the CTRC but must undergo independent review at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to the CTRC before the site is initiated and patients recruited.

Consent from the patient should be obtained prior to participation in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. A Patient Information Sheet and Consent Form (PISC) should also be implemented. The right of the patient to refuse consent to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all

patients participating in CTRC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience in obtaining informed consent. Where appropriate, age-and-stage-of-development appropriate Patient Information Sheet and Consent forms (PISC), describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document.

Upon reviewing the document, the investigator will explain the research study to the patient. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided within the PISC.

The patients will then sign and date the informed consent document. Both the person taking consent and the participant must personally sign and date the form. A copy of the informed consent document will be given to the patient for their records. The original copy will be filed in the participant's notes and a further copy of the signed consent form will be retained in the investigator site file. One final copy of the consent form should be sent to the coordinating centre to be received no later than 7 days after informed consent is received.

Participants will be invited to participate in the trial at their clinical visit. Consent will be sought at this initial visit as there are no immediate routine follow up visits. Where participants request longer to consider their decision about whether to participate the local research team will manage this. Potential participants can be invited to return to the clinic to provide consent at a later date but the cost of attending this visit will not be reimbursed as part of the trial. This is a reflection of current NHS practice in which a patient would be given their treatment options and, in consultation with their healthcare provider at that same appointment, would make a decision about how they wished to proceed.

The participant may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

In the event that the study is discontinued, participants will be treated according to usual standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in section 5.3.

12 REGULATORY APPROVAL

12.1 Statement of Compliance

Statement of compliance: The study will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (1996),
- CTRC Clinical Trials Research Centre Standard Operating Procedures
- International Conference on Harmonisation Good Clinical Practice (ICH GCP) http://www.ich.org/ (accessed 11/2014)
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- UK Policy Framework for Health and Social Care Research

SI /EU Regulation	Title	Main impact/scope
2001/20/EC	The EU Clinical Trials Directive	National Competent Authority Ethics Framework GCP legal requirement Good Manufacturing Practice Protocol/Amendments/safety Protection of Vulnerable Groups Consent / Data protection
2004/1031	Medicines for Human use Clinical Trials Regulation	Transposed EU CT Directive in UK
2005/28/EC	EU Good Clinical Practice (GCP) Directive	Investigator brochure Archiving Mandatory training for trial teams
2006/1928	Amends 2004/1031	Investigator brochure /essential documents Serious Breach Declaration of Helsinki 1996 version for CTIMP
2006/2984	Amends 2004/1031	Consent for incapacitated adult by legal representative or emergency deferred consent
2008/941	Amends 2004/1031	Blood safety and quality Emergency Deferred consent for children
2009/1164	Miscellaneous Amendment	Urgent Safety measures
2009/3063	Amends 2004/1031	Nurse and pharmacists to prescribe unlicensed medicines

12.2 Regulatory Approval

This trial falls within the remit of the 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 as amended. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is 21322/004/001-0001; the EudraCT number is 2014-002751-25.

12.3 Protocol Deviations and Serious Breaches

Incidence of protocol non-compliance are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

A breach of the protocol or GCP is ‘serious’ if it meets the regulatory definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. All serious breaches of GCP or protocol will be reported to the MHRA and REC in an expedited manner by the sponsor or agreed delegate.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the CTRC who will in turn notify the sponsor. The sponsor will assess the breach and determine if is meets the criteria of a ‘serious’ breach of GCP or protocol and therefore requires expedited reporting to the MHRA and REC.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC). In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice form the Trial Statistician. However, the sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to the MHRA and REC within 7 days by the sponsor or agreed delegate and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the sponsor, TMG, TSC, IDSMC, REC or MHRA, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial and will be described in a separate, detailed, trial monitoring plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment

In accordance with the CTRC SOP TM005 a risk assessment is completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- CTRC Director

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur. The outcome of the risk assessment will be expressed as a percentage, assigned according to the following categories:

- Score ≤ 33% = Low risk
- Score ≥ 34 to ≤ 67% = Moderate risk
- Score ≥ 68 to ≤ 100% = High risk

The level of risk assigned to the NERVES trial is documented and informs the trial specific monitoring plan.

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs (19) propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

The NERVES trial will compare two interventions that are both currently in use as part of standard care. The steroid used in the TFESI arm will be used off-label; however, this is routinely performed in standard clinical practice. As such the trial is considered to be Type A.

13.2 Source Documents

***Source data**: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
***Source documents**: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes).
Identified source documents other than the CRF for this trial are:

- Hospital records e.g. patient notes / theatre notes
- Patient administration systems

Therefore, for data where no prior record exists and which is recorded directly in the CRF the CRF will be considered the **source document** unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent (plus assent where appropriate and if taken) process including date of provision of patient information, registration number, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.

13.3 Data Capture Methods

Data will be collected on paper case report forms (CRFs) and via participant completed diaries. CRFs will be sent into CTRC for data entry into the study specific database by members of the Data Management Staff delegated with data entry responsibilities. Completed CRFs should be returned to CTRC within 3 weeks of the visit date.

13.3.1 Case Report Forms

The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained.

If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D".

If the item is not applicable to the individual case, write "N/A".

Or if the data item is un-known, write “NK”.

If a data item has not been recorded on source data then write ‘NR’.

All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. Do not erase or white-out errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRF completion guidelines will be provided to all trial sites to assist in the completion of trial CRFs.

13.3.2 Patient Completed Data

The participant randomisation number should be clearly labelled on all documents. For postal questionnaires the research team should ensure the randomisation number and any other relevant information requested is completed *before* issuing to participants. Questionnaires will be returned by the participant sending the questionnaire directly to the CTRC. For further details on the administration of the questionnaires refer to section 8.4

13.4 Central Monitoring

Data stored at CTRC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTRC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Central checks of consent will be completed for each participant to ensure the completeness of consent and that the timing of consent is in line with the protocol.

There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data which are to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g., patient records, laboratory reports, appointment books, etc. Investigators at trial sites will permit trial related monitoring activities, regulatory inspections etc. by providing this access.
Since this affects the patient’s confidentiality, this fact is included on the Participant Information Sheet and Informed Consent Form.

13.6 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Case report forms will not contain details of participant names and will be labelled with the unique trial screening and/or randomisation number instead. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Trial data collected on paper will be sent to the CTRC and stored securely in a dedicated area of the CTRC office which is locked separately to the main office. Paper copies of the consent form will be sent to the CTRC separately to any trial data. Likewise all CRFs received at the CTRC will be stored separately to consent forms.

The CTRC will be undertaking activities requiring the transfer of identifiable data.
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the CTRC by recruiting centres; this requires that name data will be transferred to the CTRC.
In order to obtain resource use data from electronic routine administrative databases, the following personal identifying data will be collected: participant name, NHS number, postcode, date of birth, and gender. This will be stored separately to the clinical data in an encrypted format with controlled access limited to appropriately delegated staff.
Any necessary transfer of identifiable data is disclosed in the PISC. The CTRC will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.7 Quality Assurance and Control

Quality Assurance (QA) includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. QA activities include, but are not limited to:

- Data will be evaluated for compliance with protocol, data accuracy and data consistency.
- The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol.
- The study will be conducted in accordance with procedures identified in the protocol.
- Monitoring activities are completed according to the agreed trial monitoring plan.
- Completion of a green light checklist to verify that all approvals are in place prior to trial initiation at the CTRC and at individual site.
- Attendance of research team (Principal Investigator, Research Nurse, and representative of neurosurgery/pain management as applicable as a minimum) from each participating centre at site initiation training. This will include training on aspects of the trial specific protocol.
- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

In accordance with the monitoring plan, centre visits will be conducted and source data verification performed if indicated to be required as a result of central monitoring processes.

13.8 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) such as the Investigator Site File until the Clinical

Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTRC will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

NERVES is sponsored by The Walton Centre NHS Foundation Trust and co-ordinated by the CTRC in the University of Liverpool. The Walton Centre NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This trial is funded by the Health Technology Assessment department of the National Institute of Health Research. Contractual agreements will be in place between sponsor and collaborating centres that will incorporate financial arrangements. As the study is funded by the NIHR HTA it will be adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs as required.

Trial participants will not be paid to participate in the trial. The schedule of the study will be in line with routine standard care apart from the 54 week post-randomisation study visit. Patients will be able to claim travel expenses for attendance at the 54 week visit upon provision of a receipt.

As the study is funded by the NIHR HTA, it will automatically be adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs if required.

15.1 Financial Support to Collaborating Centres

15.1.1 Payment to sites

Funding will be provided to sites on a per patient basis in order to facilitate recruitment, data collection and other research activities.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC. The TMG will be responsible for the day-to-day running and management of the trial and will meet regularly throughout the trial. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will have an independent chairperson and will consist of independent experts in the field of pain and neurosurgery, an independent biostatistician and a lay representative. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, an expert in the field of pain, plus 2 independent members: one who is an expert in the field of neurosurgery and one who is an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s), Health Economist(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 8.0 (10/04/2019) – Substantial Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
2 & 5	Contact details	Change in lead Sponsor contact / signatory
11	Protocol Summary	Correction of typographical error, amended study duration from “54 – 60 weeks” to “54 – 62 weeks”
21	Patient transfer and withdrawal	Section updated to reflect current withdrawal status i.e. it is only possible to withdraw up to the point that data analysis starts
51	Regulatory Approval	Change from “Research Governance Framework 2005 “to “UK Policy Framework for Health and Social Care Research”

18.2 Version 7.0 (25/10/2017) – Substantial Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
3	Statement of compliance	Moved into new section; Section 12.1
4	Contact details	Amendment made to the Trial Management and Monitoring contact details
5	Contact details	Additional Sponsor authorised individual added
6	Table of contents	Amended to reflect changes in protocol
	Glossary	Additional acronyms added; DSUR, EUDRACT, HRA, RSI, SOP, USM
	1	Target population changed from 200 to 148 Eligibility criteria change: “patient willing and able to give consent changed to “patient has provided written, informed consent”
	1	Study duration changed from “54 weeks” to “54-60 weeks”
	1	Schematic of study design updated for clarity
	2.1	Categorisations of sciatica amended for consistency
	2.2	Minor clarifications
	2.4.1	Removal of “Main Risks” lists – referred to Section 10 for safety information
	3.1	Addition of requirement for evidence of signed site:sponsor contract at CTRC and Site Suitability Assessment completion
	5.	Section separated into 3 sections: Discontibuation of trial treatment, complete withdrawal and patient transfers. Some text added: Clarification of “duration of symptoms” in cases of episodic symptoms Example of voluntary withdrawal added “e.g., patient decides not to have the randomised treatment for any reason” Responsibilities in case of patient transfer clarified
	6	Minor amendments for clarity throughout section
	6.1	Justification for short timeframe to consider consent added
	7	Minor amendments for clarity throughout section
	7.2	List of accepted active ingredients for use in TFESI arm added
	7.2	Table of expected maximum doses for each active ingredient used in TFESI arm added
	7.5.2	Addition of sentence for clarity: “As NERVES is a pragmatic trial the interventions are expected to reflect local NHS policy and so variation within the interventions is expected.”
	8	Minor amendments for clarity and to emphasise importance of data collection throughout section
	8.1	Treatment visit section added clarifying assessments and procedures

8.1	Section added providing guidance on what should be done where participants do not attend weeks 18 and 54 visits
8.1	Option for collection of Week 18 primary outcome data to be collected by telephone as 'last resort' added
8.1	Addition of Table 1: Case Report Form Completion Schedule
8.1	Addition of Table 2: Case Report Form Return Schedule
8.1	Table 1: Trial Assessments changed to Table 3: Trial Assessments
8.4.2	Expansion of Health Economics section to provide further detail and clarity regarding data handling and processing
8.4.3	'Pregnancy' section added allowing assessment of pregnancy throughout trial
8.6	Statement added clarifying patients shouldn't be withdrawn unless specifically requested
9.4.2	'Revised Sample Size' section added
10	Pharmacovigilance section modified throughout for clarification
10.1	- 'Adverse Reaction' defined for NERVES - 'Unexpected Adverse Reaction' defined for NERVES
10.3	- Unrelated AE's clarified as not reportable - TFESI causality reporting requirements clarified
10.4	Definitions and responsibilities defined for assessment of expectedness; CI responsibility (not PI) based on Relevant Safety Information available at the time
10.4	Expected Adverse Event tables reworked for clarity; split into TFESI (procedure/ IMPs) and Microdiscectomy (procedure/general anaesthetic)
10.4	Addition of expected adverse events "anaphylaxis" and "low pressure headache" added to Expected Adverse Event tables
10.6	'Overdose of any medication without signs or symptoms' added to non-reportable list
10.7	Safety reporting period defined as "from intervention up to and including the Week 54 follow up visit"
10.7	Process for completing SAE forms amended as per CTRC processes
10.8.3	'Urgent Safety Measures' section added
11.3	Minor amendment for clarity and to justify short timeframe for considering consent
12.1	'Statement of Compliance' section added
12.3	'Protocol Deviations and Serious Breaches' section added

18.3 Version 6.0 (21/03/2016) – Substantial Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
2	Signatures	Updated statisticians contact details
4	Contact details	Amendment made to the Trial Management and Monitoring contact details
10	Protocol summary	Inclusion and exclusion criteria of duration of symptoms changed from 6 months to12 months
14	Rationale	Addition of CT scanning for guidance of the TFESI injection
16	Risk and Benefit	2.4.2 Known Potential Benefits: Addition of wording in the final sentence to allow duration of non-trivial pain symptoms `up to a maximum of 12 months`
19	Study Population	Eligibility criteria of duration of symptoms changed from 6 months to12 months
27	Assessments and procedures	Added sections 8.1. New wording has been added to outline the procedures for follow-ups at weeks 18, 30, 42 and 54. Information has been included to provide clarification about the process for dealing with DNAs at weeks 18 and 54.
30	Other Assessments	Removal of duplicated information.
36	Expectedness	Added a sentence to clarify that the chief investigator will undertake the assessment of expectedness Addition of `Reoccurring prolapse of the disc` to expected list of events for microdiscectomy' Table .

38/39	Reporting Procedures	Clarified reporting processes. The process of reporting adverse events has been reduced to one flow chart to clarify the procedure (Figure 1). Figures 1&2 removed from the protocol and added new flow chart that also includes requirements to report pregnancies and any deaths.
40	Responsibilities	Removal of the trial co-ordinator's telephone number and change of the fax number for SAEs to: 0151 282 4721

18.4 Version 5.0 (19/08/2015) – Minor Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
2	Signatures	Addition of Dr. G. Burnside as Senior Statistician for on signatures page
25	Trial Treatments	Addition of information on the Ionising radiation and the levels of exposure for participants

18.5 Version 4.0 (05/05/2015) – Minor Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
Throughout		Minor clarifications and corrections of typographical errors.
5	Contacts	Medical Expert (2) contact details updated
6-8	Table of Contents	Amended to reflect changes in protocol
9	Glossary	'NHS' and 'RUSAE' added. Typographical errors amended.
10	1	Inclusion criteria: - "Newly diagnosed lower extremity radiculopathy (sciatica)" changed to "Diagnosed lower extremity radiculopathy (sciatica)" - "Severe leg pain non-responsive to conservative, non-invasive management" changed to "Leg pain non-responsive to conservative, non-invasive management" Exclusion criteria: - "Neurological deficit (foot-drop/possible cauda-equina compression)" changed to "Serious neurological deficit (e.g. foot-drop/possible cauda-equina compression) Description of Agent / Intervention: "(see Section 7 for further information)" added
12		Schematic of study design: Physical exam added at 18 week time point as per routine practice.
15	2.3	"…prior to commencement of recruitment at the remaining sites" changed to "as part of an initial feasibility study"
17	3.1	The following centre inclusion criteria have been added: a. TFESI performed according to protocol requirements (i.e., specified pharmaceutical agents available from pharmacy via local routine prescription routes) b. Able to provide both treatments within 12 weeks of randomisation c. Principal Investigator can be either a representative of neurosurgery or pain management; both specialties should be represented within the local research team
19	5.1	Point a) changed (as per Section 1 (see above)) Point d) changed (as per Section 1 (see above))
19	5.2	Point a) changed (as per Section 1 (see above))
21	6.3	Timelines for performing randomisation clarified
23	7.2	Clarification of an expected TFESI regimen, reference to MHRA labelling exemption and "Treatment must occur within 12 weeks of randomisation to ensure valid collection of primary outcome data at the 18 week follow up" added.
24	7.3	"Treatment must occur within 12 weeks of randomisation to ensure valid collection of primary outcome data at the 18 week follow up" added.
24	7.4	Additional text to clarify crossover is acceptable prior to receiving randomised treatment.

27	8: Table 1	‘Physical exam’ and ‘Assessment of additional interventions’ added at T = 18 weeks ‘Assessment of additional interventions added for Unscheduled Visits. Removal of “If necessary, data collection can occur via telephone”
36-38	10	Addition of text to clarify adverse event reporting requirements and the classifications of ‘reactions’ (related to IMP) versus ‘events’ (related to procedures).
46	13.2	Additional examples of source data added
48	13.7	Suggestion of additional local research team members for site training
52	16.1	“Approximately 3 times a year” changed to “regularly throughout the trial” for TMG meetings
	16.2	Membership format of TSC clarified

18.6 Version 3.0 (15/12/2014) – Minor Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
N/A	Header	Addition of header to signature page
Throughout	Throughout	"After randomisation" added to references to timepoints
10	1	Inclusion criteria: - "Newly diagnosed sciatica secondary to PID (proven on MRI)" changed to "Newly diagnosed lower extremity radiculopathy (sciatica) - Diagnosed with lower extremity radiculopathy (sciatica) secondary to a lumber disc herniation" changed to "Sciatica secondary to prolapsed intervertebral disc (PID) (proven on MRI) - Criteria addressing conservative treatments (medication, modification of daily activities and physiotherapy) have been combined to "Patient has attempted at least one form of conservative (non-operative) treatment* but this has not provided adequate relief of patient's pain/symptoms *including but not limited to; medication, physiotherapy, modification of daily activities"
10	1	Exclusion criteria: - "Pregnancy" changed to "Patient known to be pregnant" - "Not attempted conservative non-operative treatment for a minimum of 6 weeks" changed to "Patient has not attempted any form of conservative treatment"
10-11	1	Secondary outcome amended: - "work status" removed
12	1	Schematic of study design – timepoint assessments added that had been missed in error
18	4.2	Point g) "and work days lost if applicable" added
18	4.3	Typographical error amended – removal of (
19	5.1	Point a) changed (as per Section 1 (see above)) Point e) changed (as per Section 1 (see above)) Points f)-h) combined (as per Section 1 (see above))
19	5.2	Point d) changed (as per Section 1 (see above)) Point e) changed (as per Section 1 (see above))
25	8.1	Return to work added to Table of Assessments
25	8.1	54 week follow up window extended from 58 to 62 weeks Removal of statement that 54 week window will capture 12 months post-intervention as this is not guaranteed
27	8.4.1	"Standardised questionnaires" changed to "patient reported outcome measures"
27	8.4.1	"Numerical rating score for leg and back pain" added to list
34	10.4	AEs added to table 3 (related to steroid agent/anaesthetic agent)
34	10.4	Table 4 added to list events associated with general anaesthetic
35	10.6	Removal of requirement for investigator to make an assessment of expectedness when recording Adverse Events
35	10.6	"Additional TFESI or microdiscectomy surgery arising from patient crossover" added to list of 'Do not include' when reporting SAEs
37-38	10.7	Removal of "Current Status" from minimum information required for SAE reporting Change of "patient number" to "participant number" Removal of "Whether study treatment was discontinued"
38	10.8	Correction of formatting error
39	10.8.1	Text added: "The CTRC will notify the main REC of all RUSAEs occurring during the study not later than 15 days after being made aware of the event."
41	11.3	"within 7 days of the visit date" added to define when consent forms must be returned to the CTRC
50	16.2	"up to seven principal investigators" changed to "a lay representative"

18.7 Version 2.0 (30/09/2014) – Minor Amendment

Page Number	Section	Change
Throughout	Header	Updated to reflect version change
Throughout	N/A	'MCRN CTU' changed to 'CTRC' or 'MC CTU' as appropriate
Throughout	N/A	References to "Roland-Morris scale" – 'scale' amended to 'score'
6-8	Table of Contents	Amended to reflect changes in protocol
9	Glossary	Addition of 'CT' and 'XR' definition
10	1	Inclusion criteria: - removal of 'disabling' from "newly diagnosed disabling sciatica…" - addition of 'and able' to "patient willing to give consent"
10	1	Exclusion criteria: - Addition of "Sciatica presentation for longer than 6 months" - Addition of 'and/or injection' to "…contraindication for surgery" - Addition of "Pregnancy" as a specific exclusion criterion
12	1	Schematic of Study Design: - Addition of EQ-5D-5L at Screening, 18, 30, 42 and 54 weeks - Addition of Return to Work at 18 and 54 weeks
18	4.3	Text edited for clarity
19	5.1	Point a) removal of 'disabling' from "newly diagnosed disabling sciatica…"
19	5.1	Point c) "Symptoms" changed to "Severe leg pain"
19	5.1	Points g) and h) added to align with Section 1
19	5.2	Point b) addition of 'spinal' and 'same intervertebral disc' for clarification
19	5.2	Point f) '12 months' corrected to '6 months' in line with Inclusion Criteria
19	5.2	Point i) "Any contraindication for injection" added
19	5.2	Text added to describe assessment of contraindication as per routine care
19	5.3	Minor text amendments for clarification
23	7.2	Addition of an example of an acceptable treatment regimen
23	7.2	Addition of text regarding repeat injections to clarify that repeat injections for Arm A patients are acceptable as per local policy and that data are recorded
24	7.4	Section formatting - 7.4 Cross Over Between Trial Treatments
24	7.4	Minor text amendments to clarify crossover and describe process if participants receive further treatment for sciatica
25	8	Typographical error "retuned" removed
26	8.1	Table 1: - Addition of EQ-5D-5L to 'Procedures' list - Addition of Unscheduled Visits to the schedule
27	8.2	Outcome measures defined as points i) – ix)
27	8.4.1	Correction - EQ-5D-5L not required at treatment visit
27	8.4.1	Clarification - Questionnaires to be returned directly to CTRC
31	9.5.2	Clarification of timelines for IDSMC meetings
32-41	10	Various minor text changes throughout to clarify section
634	10.4	Table 3 events split into A and B for clarity
34-35	10.4-10.6	Change 'table 3' to 'Table 3'
34	10.4	'Drug' removed from "Adverse Drug Reaction" so that AE definition covers reactions to surgical intervention
35	10.6	Typographical error 'Table X' to 'Table 3'
36	10.2	Hyperlink error removed – replaced with '10.1'
36	10.6	Figure 1 updated to refer to Table 3 and clarify reporting procedures for TFESI arm
37	10.6	Figure 2 updated to refer to Table 3 and clarify reporting procedures for surgical arm
37	10.7	Addition of 'Site' to define "Responsibilities – Investigator"
38	10.7 ii	Update to trial co-ordinator telephone number
38	10.7 vi	vi unbolded
41	11.2	Addition of specific REC details
43	12	Addition of CTA and EudraCT detail
45	13.2	Addition of 'Screening Log' and 'Informed Consent' as source documents
46	13.4	Removal of reference to unblinding as NERVES is not a blinded trial

18.8 Version 1.0 (27/06/2014)

Original Approved version.

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

The following supplementary documents accompany the protocol and are separately updated and version controlled:

- Patient Information Sheet and Consent form (PISC)
- Patient Questionnaires
- Participating centres list
- GP letter