Clinical trial results:
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)

Summary

EudraCT number	2014-002751-25
Trial protocol	GB
Global end of trial date	09 July 2019

Results information

Result version number	v1 (current)
This version publication date	18 July 2020
First version publication date	18 July 2020
Summary attachment (see zip file)	NERVES stats analysis report (NERVES Final Analysis Report v2.0 20191205.pdf)

Trial information

Trial identification

Sponsor protocol code	RG112-14

Additional study identifiers

ISRCTN number	ISRCTN04820368
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Walton Centre NHS Foundation Trust
Sponsor organisation address	Lower Lane, Liverpool, United Kingdom, L9 7LJ
Public contact	NERVES Trial, Liverpool Clinical Trials Centre, University of Liverpool, 0044 151 7949768, nerves@liverpool.ac.uk
Scientific contact	NERVES Trial, Liverpool Clinical Trials Centre, University of Liverpool, 0044 151 7949768, nerves@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2019
Global end of trial reached?	Yes
Global end of trial date	09 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to provide evidence to potentially inform future treatment of sciatica secondary to prolapsed disc. Transforaminal epidural steroid injection is recognised as a treatment alternative to surgical microdiscectomy, but it is not known how effective and cost effective this treatment is in comparison. This trial will compare the epidural steroid injection and microdiscectomy, and examine the impact of the different treatments on several outcomes such as Oswestry Disability Questionnaire scores, other back and leg pain questionnaires, and health economic analyses.

The primary outcome will be the Oswestry Disability Questionnaire (ODQ; a condition specific outcome measure with over 30 years of scientific validation) at 18 weeks follow up (approx. 3 months after treatment).

Protection of trial subjects:

The written informed consent and the completed baseline CRF to confirm and assess eligibility was authorised by an appropriately qualified doctor. Participants were 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 were completed prior to randomisation but after provision of consent.

Background therapy:

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

Evidence for comparator:

Surgical microdiscectomy for acute sciatica.

Actual start date of recruitment	04 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 163
Worldwide total number of subjects	163
EEA total number of subjects	163

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	162
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial took place in 12 centres; 11 centres randomised at least 1 participant. Patients were recruited from units receiving patients from pooled tertiary referrals from GPs, allied health professionals and non-spinal consultants. The first patient was randomised on 06 March 2015 and the last patient was randomised on 21 December 2017.

Pre-assignment

Screening details:

A total of 1055 subjects were assessed for eligibility, of which 892 subjects were excluded. Of these, 723 subjects did not meet the inclusion criteria, 168 subjects declined and 1 value was missing. This left a total of 163 subjects to be randomised.

Pre-assignment period milestones

Number of subjects started	1055[1]
Number of subjects completed	163

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting inclusion criteria: 723
Reason: Number of subjects	Eligiblity yes/ no missing: 1
Reason: Number of subjects	Not approached/ declined to participate: 168

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients who started the pre-assignment period (screened - 1055) is larger than the number who enrolled in the trial (randomised -163).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Surgery

Arm description:

Standard surgical lumbar microdiscectomy.

Arm type	Standard microdiscectomy

No investigational medicinal product assigned in this arm

Arm title	TFESI

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	TFESI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Epidural use

Dosage and administration details:

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

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

Number of subjects in period 1	Surgery	TFESI
Started	83	80
Completed	83	80

Baseline characteristics

Reporting groups	
Reporting group title	Surgery
Reporting group description:	
Standard surgical lumbar microdiscectomy.	
Reporting group title	TFESI
Reporting group description:	
Fluoroscopically guided trans-foraminal epidural steroid injection (TFESI) of a standard combination of local anaesthetic and steroid drug.	

Reporting group values	Surgery	TFESI	Total
Number of subjects	83	80	163
Age categorical			
The numbers of subjects within each age category on both treatment arms.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	82	80	162
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
The mean and standard deviation of the ages of subjects on both treatment arms.			
Units: years			
arithmetic mean	43.5	41.2	
standard deviation	± 9.9	± 8.6	-
Gender categorical			
The number of males and females allocated to both surgery and injection.			
Units: Subjects			
Female	46	40	86
Male	37	40	77
Reproductive potential			
The number of female participants who are of reproductive potential.			
Units: Subjects			
No	11	5	16
Yes	35	35	70
N/A	37	40	77
Taking Anticoagulant Medication			
The number of participants allocated to both surgery and injection taking any anticoagulant medication at the time of randomisation.			
Units: Subjects			
No	82	79	161
Yes	1	1	2
Previous surgery at disc level			

Data on whether or not the patient previously had surgery at the same intervertebral disc (Level).			
Units: Subjects			
No	82	80	162
Yes	1	0	1
Has patient taken medication for pain and symptoms?			
Has the patient used medication to help treat pain and symptoms?			
Units: Subjects			
No	83	80	163
Yes	0	0	0
Has patient modified activity?			
Has the patient modified daily activities to help pain and symptoms?			
Units: Subjects			
No	0	1	1
Yes	83	79	162
Has patient attended physiotherapy?			
Has the patient attended physiotherapy to help pain and symptoms?			
Units: Subjects			
No	15	16	31
Yes	68	64	132
Has patient had other conservative (non operative) treatment for pain and symptoms?			
Has the patient had other conservative (non operative) treatment to help pain and symptoms?			
Units: Subjects			
No	49	43	92
Yes	34	37	71
Estimated volume of canal occupied by disc prolapse			
Estimated volume of canal occupied by disc prolapse as shown on MRI scan.			
Units: Subjects			
Less than 25%	43	44	87
Between 25%-50%	36	34	70
Greater than 50%	4	2	6
Posture			
Data on whether or not the posture of each participant is normal.			
Units: Subjects			
Abnormal	38	41	79
Normal	43	37	80
Not done	2	2	4
Range of movement			
Data on whether or not the range of movement of each participant is normal.			
Units: Subjects			
Abnormal	52	50	102
Normal	27	27	54
Not done	4	3	7
Muscle strength			
Data on whether or not the muscle strength of each participant is normal.			
Units: Subjects			
Abnormal	12	18	30
Normal	67	59	126
Not done	4	3	7

Left ankle jerks present			
Data on whether or not left ankle jerks were present.			
Units: Subjects			
No	13	11	24
Yes	68	66	134
Data unobtainable	2	3	5
Right ankle jerks present			
Data on whether or not right ankle jerks were present.			
Units: Subjects			
No	13	13	26
Yes	68	66	134
Data unobtainable	2	1	3
left knee jerks present			
Data on whether or not left knee jerks were present.			
Units: Subjects			
No	2	4	6
Yes	79	73	152
Data unobtainable	2	3	5
Right knee jerks present			
Data on whether or not right knee jerks were present.			
Units: Subjects			
No	3	5	8
Yes	78	74	152
Data unobtainable	2	1	3
SLR reduction present			
Data on whether or not a SLR reduction took place.			
Units: Subjects			
No	6	4	10
Yes	75	76	151
Data unobtainable	2	0	2
Location of SLR reduction present			
Data on the location of the SLR reduction.			
Units: Subjects			
Bilateral	7	9	16
Unilateral (left)	37	39	76
Unilateral (right)	31	28	59
N/A	8	4	12
Any other abnormalities present			
Any other abnormalities noted during the physical examination?			
Units: Subjects			
No	63	59	122
Yes	19	21	40
Data unobtainable	1	0	1
Is patient currently employed?			
Is the patient currently employed?			
Units: Subjects			
No	21	13	34
Yes	62	66	128
Data unobtainable	0	1	1
Is patient currently unable to work due to sciatica			

Is the patient currently unable to attend work due to sciatica?			
Units: Subjects			
No	41	34	75
Yes	21	32	53
N/A	21	14	35
Is the patient is currently taking analgesics/ steroids/ anticoagulant medication?			
Is the patient currently taking analgesics, steroids or anticoagulant medication?			
Units: Subjects			
No	7	7	14
Yes	76	73	149
Duration of symptoms Summary			
Units: Weeks			
arithmetic mean	21.5	21.1	
standard deviation	± 10.7	± 11.2	-
Weight			
Units: kilogram(s)			
arithmetic mean	83.7	81.4	
standard deviation	± 16.8	± 20.7	-
Height			
Units: centimetres			
arithmetic mean	171.7	172.6	
standard deviation	± 10.7	± 9.5	-
BMI			
Units: kilogram(s)/square meter			
arithmetic mean	28.2	27.2	
standard deviation	± 5.3	± 6.4	-

End points

End points reporting groups

Reporting group title	Surgery
Reporting group description:	
Standard surgical lumbar microdiscectomy.	
Reporting group title	TFESI
Reporting group description:	
Fluoroscopically guided trans-foraminal epidural steroid injection (TFESI) of a standard combination of local anaesthetic and steroid drug.	
Subject analysis set title	ODQ Extended Model Surgery
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the surgery arm included in the extened model for ODQ	
Subject analysis set title	ODQ Extended Model TFESI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the TFESI arm included in the extened model for ODQ	
Subject analysis set title	ODQ Sensitivity MI Surgery
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the surgery arm included in the sensitivity analyis of the primary outcome using multiple imputations.	
Subject analysis set title	ODQ Sensitivity MI TFESI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the TFESI arm included in the sensitivity analyis of the primary outcome using multiple imputations.	
Subject analysis set title	ODQ post-hoc Model Surgery
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the surgery arm included in the post-hoc extened model for ODQ which also included level of disc prolapse	
Subject analysis set title	ODQ post-hoc Model TFESI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of subjects in the TFESI arm included in the post-hoc extened model for ODQ which also included level of disc prolapse	

Primary: ODQ (primary outcome)

End point title	ODQ (primary outcome)
End point description:	
The primary outcome (ODQ score at 18 weeks post-randomisation) was compared between groups using a linear regression model, adjusted for the stratification variable centre, baseline ODQ score, and other (specified in advance) variables considered to be potential confounders.	
End point type	Primary
End point timeframe:	
ODQ score at 18 weeks post randomisaiton (+/- 6 weeks).	

End point values	Surgery	TFESI	ODQ Extended Model Surgery	ODQ Extended Model TFESI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	61[1]	63[2]	56[3]	53[4]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	49.39 (± 17.81)	53.74 (± 19.35)	0 (± 0)	0 (± 0)
Week 18	22.30 (± 19.83)	30.02 (± 24.38)	0 (± 0)	0 (± 0)
Difference	-26.74 (± 21.35)	-24.52 (± 18.89)	0 (± 0)	0 (± 0)

Notes:

[1] - Baseline: n = 83 n missing = 0
Week 18: n = 61 n missing/ invalid = 22
[2] - Baseline: n=79 n missing=1
Week 18: n=63 n missing/invalid=17

[3] - Baseline and week 18 summaries not included for this analysis

[4] - Baseline and week 18 summaries not included for this analysis

End point values	ODQ Sensitivity MI Surgery	ODQ Sensitivity MI TFESI	ODQ post-hoc Model Surgery	ODQ post-hoc Model TFESI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83[5]	79[6]	54[7]	52[8]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Week 18	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Difference	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Notes:

[5] - Baseline and week 18 summaries not included for this analysis

[6] - Baseline and week 18 summaries not included for this analysis

[7] - Baseline and week 18 summaries not included for this analysis

[8] - Baseline and week 18 summaries not included for this analysis

Statistical analyses

Statistical analysis title	ODQ primary analysis

Statistical analysis description:

The primary outcome (ODQ score at 18 weeks post-randomisation) was compared between groups using a linear regression model, adjusted for the stratification variable centre and baseline ODQ score.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.09
upper limit	2.59

Statistical analysis title	ODQ Extended model

Statistical analysis description:

As well as the model specified for our primary outcome analysis, we also considered if any of the following baseline variables adjusted our estimate of treatment effect by adding them to our mixed effects model as fixed effects: Age, Sex, BMI, Duration of symptoms, Estimated volume of canal occupied.

Comparison groups	ODQ Extended Model TFESI v ODQ Extended Model Surgery
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1991
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.76
upper limit	2.7

Statistical analysis title	ODQ primary analysis - Sensitivity

Statistical analysis description:

Sensitivity analyses was carried out as the amount of missing data was greater than 10%. Multiple imputation was used to assess the robustness of the analysis to missing primary outcome data.

Comparison groups	ODQ Sensitivity MI TFESI v ODQ Sensitivity MI Surgery
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.393
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.16
upper limit	3.99

Notes:

[9] - Sensitivity analyses

Statistical analysis title	ODQ Extended model - post-hoc

Statistical analysis description:

As well as the model specified for our primary outcome analysis, we also considered if any of the following baseline variables adjusted our estimate of treatment effect by adding them to our mixed effects model as fixed effects: Age, Sex, BMI, Duration of symptoms, Estimated volume of canal occupied. As a post-hoc analysis the level of disc prolapse was also added to this model.

Comparison groups	ODQ post-hoc Model Surgery v ODQ post-hoc Model TFESI

Number of subjects included in analysis	106
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.215
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.81
upper limit	2.93

Secondary: Secondary efficacy endpoint 1 – ODQ (18, 30, 42, 54 weeks)

End point title	Secondary efficacy endpoint 1 – ODQ (18, 30, 42, 54 weeks)

End point description:

Change from baseline summaries (ODQ score at follow up - baseline) are presented in this section where both the baseline ODQ questionnaire and follow up questionnaire were completed. A lower ODQ scores represents lower levels of disability therefore a decrease from baseline represents an improvement. Questionnaires are only included in the summaries if they were completed at the protocol specified time points post randomisation (+/- 2 weeks for week 18, week 30 and week 42 and 54-62 weeks for week 54 questionnaire). The study design defines questionnaires to be measured a specific time-points, however measurements that are not taken at per-protocol time-points were still included in this mixed model analysis as the time in weeks was included in the model to directly account for the time between baseline and completed follow up questionnaires. The ODQ is only considered valid if at least 8 out of 10 items were answered.

End point type	Secondary

End point timeframe:

Weeks 18, 30, 42 and 52 post randomisation

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75[10]	72[11]		
Units: Scores				
arithmetic mean (standard deviation)				
Week 18 ODQ summary	-27.18 (± 22.31)	-24.29 (± 18.28)		
Week 30 ODQ summary	-26.62 (± 19.12)	-23.25 (± 17.45)		
Week 42 ODQ summary	-31.40 (± 17.22)	-25.51 (± 23.74)		
Week 54 ODQ summary	-30.38 (± 17.77)	-31.10 (± 24.35)		

Notes:

[10] - 18 n=46 n inval/miss=37
30 n=40 n inval/miss=43
42 n=40 n inval/miss=43
54 n=48 n inval/miss=35
[11] - 18 n=51 n inval/miss=29
30 n=30 n inval/miss=50

42 n=34 n inval/miss=46
54 n=42 n inval/miss=38

Statistical analyses

Statistical analysis title	Parameter estimates for ODQ longitudinal model

Statistical analysis description:

A repeated measures random effects model was fitted. The dependent variable was post baseline ODQ. Covariates were: baseline ODQ, treatment arm, time (fitted as a continuous variable), and a time-treatment arm interaction. Centre was fitted as a random effect. The time-treatment interaction was dropped if it was found to be non-significant ($p<0.05$).

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.61
upper limit	1.28

Notes:

[12] - A time-treatment interaction was tested and was found to be non-significant so was excluded from the model, below the treatment effect (estimated mean difference in ODQ) is reported together with a 95% CI and a p-value.

Statistical analysis title	Post-hoc: parameter estimates for ODQ joint model

Statistical analysis description:

As a post-hoc analysis, joint modelling of the longitudinal outcome (as above) and the time to study dropout was done to consider the possibility of informative dropout. The longitudinal model was fitted as mixed effects model with a random intercept and random slope for participant. The parameter estimates are found below, the standard errors were calculated from 246 bootstrapped samples (4 failed to converge).

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	147
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.108
Method	Joint modelling
Parameter estimate	Mean difference (final values)
Point estimate	-4.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.84
upper limit	1.27

Secondary: Secondary efficacy endpoint 2 - Leg pain (18,30, 42 and 54 weeks)

End point title	Secondary efficacy endpoint 2 - Leg pain (18,30, 42 and 54 weeks)

End point description:

Change from baseline summaries (Numerical rating of leg pain at follow up - baseline) are presented in this section where the numerical rating for leg pain were completed. A lower leg pain rating (0-100) represents lower overall pain so a decrease from baseline represents an improvement. Questionnaires were only included in the summaries if they were completed at protocol specified time points post randomisation (+/- 2 weeks for week 18, week 30 and week 42 and 54-62 weeks for week 54 questionnaire). The study design defines questionnaires to be measured a specific time-points, measurements that are not taken at per-protocol time-points were still included in this mixed model analysis as the time in weeks was included in the model to directly account for the time between baseline and completed follow up questionnaire.

End point type	Secondary

End point timeframe:

Weeks 18, 30, 42 and 54 post randomisation

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[13]	70[14]		
Units: rating				
arithmetic mean (standard deviation)				
Week 18 leg pain summary	-58.31 (± 34.51)	-43.55 (± 32.52)		
Week 30 leg pain summary	-54.37 (± 27.05)	-42.70 (± 35.27)		
Week 42 leg pain summary	-55.81 (± 31.66)	-47.12 (± 42.28)		
Week 54 leg pain summary	-55.44 (± 33.57)	-47.08 (± 33.06)		

Notes:

[13] - 18 n=45 n inval/miss=38
30 n=38 n inval/miss=45
42 n=37 n inval/miss=46
54 n=43 n inval/miss=40
[14] - 18 n=49 n inval/miss=31
30 n=30 n inval/miss=50
42 n=33 n inval/miss=47
54 n=39 n inval/miss=41

Statistical analyses

Statistical analysis title	Leg pain longitudinal model

Statistical analysis description:

A repeated measures random effects model was fitted. The dependent variable was post baseline numerical rating scores for leg pain. Covariates were: baseline numerical rating scores for leg pain, treatment arm, time (fitted as a continuous variable), and a time-treatment arm interaction. Centre was fitted as a random effect. The time-treatment interaction was dropped if it was found to be non-significant ($p<0.05$). In addition to this, effect estimates, 95% CIs and a p-value at T18 were reported.

Comparison groups	TFESI v Surgery

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115 [15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.81
upper limit	1.73

Notes:

[15] - A time-treatment interaction was tested and was found to be non-significant so was excluded from the model, below the treatment effect (estimated mean difference in numerical rating of leg pain) is reported together with a 95% CI and a p-value.

Statistical analysis title	Parameter estimates for leg pain joint model

Statistical analysis description:

As a post-hoc analysis, joint modelling of the longitudinal outcome and the time to study dropout was done to consider the possibility of informative dropout. The longitudinal model was fitted as mixed effects model with a random intercept for participant. The random intercept and slope model failed to converge and the model improvement was marginal. The parameter estimates are found below, the standard errors were calculated from 250 bootstrapped samples.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	140
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.098
Method	Joint modelling
Parameter estimate	Mean difference (final values)
Point estimate	-7.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.82
upper limit	0.86

Secondary: Secondary efficacy endpoint 3 - Back pain (18, 30, 42 and 54 weeks)

End point title	Secondary efficacy endpoint 3 - Back pain (18, 30, 42 and 54 weeks)

End point description:

Change from baseline summaries (Numerical rating of back pain at follow up - baseline) are presented in this section where the numerical rating for back pain were completed. A lower score for back pain represents lower overall pain so a decrease from baseline represents an improvement. Questionnaires were only included in the summaries if they were completed at protocol specified time points (+/- 2 weeks for week 18, week 30 and week 42 and 54-62 weeks for week 54 questionnaire). The study design defines numerical rating for back pain be measured a specific time-points, measurements that are not taken at per-protocol time-points will still be included in this mixed model analysis as time in weeks will be included in the model to directly account for the time between baseline and follow up questionnaires

End point type	Secondary

End point timeframe:

Weeks 18, 30, 42 and 54 post randomisation.

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[16]	70[17]		
Units: Rating				
arithmetic mean (standard deviation)				
Week 18 back pain summary	-26.02 (± 32.83)	-23.41 (± 27.69)		
Week 30 back pain summary	-25.00 (± 32.04)	-24.33 (± 31.95)		
Week 42 back pain summary	-20.81 (± 37.43)	-23.00 (± 37.29)		
Week 54 back pain summary	-23.07 (± 34.54)	-22.90 (± 29.11)		

Notes:

[16] - 18 n=45 n inval/miss=38
30 n=38 n inval/miss=45
42 n=37 n inval/miss=46
54 n=42 n inval/miss=41
[17] - 18 n=49 n inval/miss=31
30 n=30 n inval/miss=50
42 n=33 n inval/miss=47
54 n=39 n inval/miss=41

Statistical analyses

Statistical analysis title	Back pain rating longitudinal model

Statistical analysis description:

A repeated measures random effects model was fitted. The dependent variable was post baseline numerical rating scores for back pain. Covariates were: baseline numerical rating scores for back pain, treatment arm, time (fitted as a continuous variable), and a time-treatment arm interaction. Centre was fitted as a random effect. The time-treatment interaction was dropped if it was found to be non-significant ($p<0.05$). In addition, effect estimates, 95% CIs and a p-value at T18 were reported.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473 [18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.29
upper limit	5.26

Notes:

[18] - A time-treatment interaction was tested and was found to be non-significant so was excluded from the model, below the treatment effect (estimated mean difference in numerical rating of back pain) is reported together with a 95% CI and a p-value.

Statistical analysis title	Parameter estimates for back pain joint model

Statistical analysis description:

As a post-hoc analysis, joint modelling of the longitudinal outcome (as above) and the time to study dropout was done to consider the possibility of informative dropout. The longitudinal model was fitted as mixed effects model with a random intercept and random slopes for participant. The parameter estimates are found below, the standard errors were calculated from 197 bootstrapped samples (53 failed to converge).

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	141
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.457
Method	Joint modelling
Parameter estimate	Mean difference (final values)
Point estimate	-2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.58
upper limit	3.16

Secondary: Secondary efficacy endpoint 4 - Likert scale for satisfaction with care

End point title	Secondary efficacy endpoint 4 - Likert scale for satisfaction with care

End point description:

The Likert scale for satisfaction with care was used to assess patients' satisfaction with the care received during the study and this was assessed at 54 weeks post randomisation. Lower scores over the 2 questions indicated higher levels of satisfaction.

End point type	Secondary

End point timeframe:

Week 54

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[19]	58[20]		
Units: scores				
median (inter-quartile range (Q1-Q3))				
week 54	1 (1 to 2)	1.5 (1 to 3)		

Notes:

[19] - n=61 n missing=22

[20] - n=58 n missing=22

Statistical analyses

Statistical analysis title	Mann-Whitney results

Statistical analysis description:

Patient treatment satisfaction scores at 54 weeks were compared between groups using the Mann-Whitney U test. A blind review of the data was undertaken and the distribution of the Likert score at 54 weeks was found to be non-normal.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Secondary: Secondary efficacy endpoint 5 - Roland-Morris (18, 30, 42, 54 weeks)

End point title	Secondary efficacy endpoint 5 - Roland-Morris (18, 30, 42, 54 weeks)

End point description:

Change from baseline summaries (Roland-Morris at follow up - baseline) are presented in this section where the modified Roland-Morris (MRM) was completed at both time points. A Lower MRM score relates to lower levels of disability so a decrease from baseline represents an improvement. Questionnaires are only included in the summaries if they were completed at protocol specified time points (+/- 2 weeks for week 18, week 30 and week 42 and 54-62 weeks for week 54 questionnaire). The study design defines numerical rating for back pain be measured a specific time-points, measurements that are not taken at per-protocol time-points will still be included in this mixed model analysis as time in weeks will be included in the model to directly account for the time between baseline and follow up questionnaires.

End point type	Secondary

End point timeframe:

Weeks 18, 30, 42 and 54 post randomisation

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[21]	72[22]		
Units: scores				
arithmetic mean (standard deviation)				
Week 18 MRM summary	-9.09 (± 6.27)	-7.73 (± 5.91)		
Week 30 MRM summary	-9.58 (± 5.60)	-7.48 (± 6.68)		
Week 42 MRM summary	-9.56 (± 5.86)	-8.35 (± 8.56)		
Week 54 MRM summary	-9.74 (± 6.65)	-9.24 (± 6.68)		

Notes:

[21] - 18 n=47 n inval/miss=36
30 n=40 n inval/miss=43
42 n=39 n inval/miss=44
54 n=47 n inval/miss=36
[22] - 18 n=51 n inval/miss=29
30 n=31 n inval/miss=49
42 n=34 n inval/miss=46
54 n=42 n inval/miss=38

Statistical analyses

Statistical analysis title	MRM longitudinal model

Statistical analysis description:

A repeated measures random effects model was fitted. The dependent variable was post baseline MRM outcome score for sciatica. Covariates were: baseline MRM outcome score for sciatica, treatment arm, time (fitted as a continuous variable), and a time-treatment arm interaction. Centre was fitted as a random effect. The time-treatment interaction was dropped if it was found to be non-significant ($p<0.05$). In addition to this, effect estimates, 95% CIs and a p-value at T18 were reported.

Comparison groups	TFESI v Surgery

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [23]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.67
upper limit	0.03

Notes:

[23] - A time-treatment interaction was tested and was found to be non-significant so was excluded from the model, below the treatment effect (estimated mean difference in MRM) is reported together with a 95% CI and a p-value.

Statistical analysis title	Post-hoc: parameter estimates for MRM joint model

Statistical analysis description:

As a post-hoc analysis, joint modelling of the longitudinal outcome (as above) and the time to study dropout was done to consider the possibility of informative dropout. The longitudinal model was fitted as mixed effects model with a random intercept and random slopes for participant. The parameter estimates are found below, the standard errors were calculated from 250 bootstrapped samples.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.063
Method	Joint modelling
Parameter estimate	Mean difference (final values)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	0.1

Secondary: Secondary efficacy endpoint 6 - COMI (18, 30, 42 and 54 weeks)

End point title	Secondary efficacy endpoint 6 - COMI (18, 30, 42 and 54 weeks)

End point description:

Change from baseline summaries (COMI at follow up – baseline COMI) are presented in this section where the numerical rating for leg pain were completed. Lower leg pain rating represents lower overall pain so a decrease from baseline represents an improvement. Questionnaires were only included in the summaries if they were completed at protocol specified time points (+/- 2 weeks for week 18, week 30 and week 42 and 54-62 weeks for week 54 questionnaire). The study design defines questionnaires to be measured a specific time-points, measurements that are not taken at per-protocol time-points were still included in this mixed model analysis as the time in weeks was included in the model to directly account for the time between baseline and completed follow up questionnaires. Only COMI questionnaires with all items answered were included in the summaries. If a COMI questionnaire was missing an item then it was recorded as missing.

End point type	Secondary

End point timeframe:

Weeks 18, 30, 42 and 54 post randomisaiton.

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[24]	67[25]		
Units: Rating				
arithmetic mean (standard deviation)				
Week 18 COMI summary	-3.93 (± 2.80)	-3.05 (± 2.69)		
Week 30 COMI summary	-4.49 (± 2.44)	-3.33 (± 2.35)		
Week 42 COMI summary	-4.92 (± 2.18)	-3.45 (± 3.14)		
Week 54 COMI summary	-5.02 (± 2.32)	-3.93 (± 2.81)		

Notes:

[24] - 18 n=42 n inval/miss=41
30 n=32 n inval/miss=51
42 n=33 n inval/miss=50
54 n=39 n inval/miss=44
[25] - 18 n=47 n inval/miss=33
30 n=27 n inval/miss=53
42 n=32 n inval/miss=48
54 n=37 n inval/miss=43

Statistical analyses

Statistical analysis title	COMI longitudinal model

Statistical analysis description:

A repeated measures random effects model was fitted. The dependent variable was post baseline COMI scores. Covariates were: baseline COMI scores, treatment arm, time (fitted as a continuous variable), and a time-treatment arm interaction. Centre was fitted as a random effect. The time-treatment interaction was dropped if it was found to be non-significant ($p<0.05$). In addition to this, effect estimates, 95% CIs and a p-value at T18 were reported.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059 [26]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	0.03

Notes:

[26] - A time-treatment interaction was tested and was found to be non-significant so was excluded from the model, below the treatment effect (estimated mean difference in COMI score) is reported together with a 95% CI and a p-value.

Statistical analysis title	Post-hoc: parameter estimates for COMI joint model

Statistical analysis description:

As a post-hoc analysis, joint modelling of the longitudinal outcome (as above) and the time to study dropout was done to consider the possibility of informative dropout. The longitudinal model was fitted as

mixed effects model with a random intercepts and random slopes for participant. The parameter estimates are found below, the standard errors were calculated from 250 bootstrapped samples.

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	132
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.046
Method	Joint modelling
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	-0.02

Secondary: Secondary efficacy endpoint 7 – Work Status (Baseline)

End point title	Secondary efficacy endpoint 7 – Work Status (Baseline)

End point description:

The number of patients that are employed/not employed at baseline are presented in this section by treatment group. Of those patients who are employed, the number of patients that are off work/at work are also presented by treatment group.

End point type	Secondary

End point timeframe:

Baseline

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	80		
Units: subjects				
Unemployed	21	13		
Employed	62	66		
Working	41	34		
Not working	21	32		
Missing/ can't tell	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary efficacy endpoint 7 – Work Status (Week 18)

End point title	Secondary efficacy endpoint 7 – Work Status (Week 18)

End point description:

The number of patients that are employed/ not employed at week 18 are presented in this section by

treatment group. Of those patients who are employed, the number of patients that are off work/at work are also presented by treatment group.

End point type	Secondary

End point timeframe:

Week 18

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	53		
Units: subjects				
Unemployed	18	16		
Employed	54	53		
Working	45	44		
Not working	6	9		
Missing/ can't tell	14	11		

Statistical analyses

Statistical analysis title	Chi-square test of association - week 18

Statistical analysis description:

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

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.449
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.81

Secondary: Secondary efficacy endpoint 7 – Work Status (Week 54)

End point title	Secondary efficacy endpoint 7 – Work Status (Week 54)

End point description:

The number of patients that are employed/not employed at week 54 are presented in this section by treatment group. Of those patients who are employed, the number of patients that are off work/at work are also presented by treatment group.

End point type	Secondary

End point timeframe:

week 54

End point values	Surgery	TFESI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	38		
Units: subjects				
Unemployed	15	13		
Employed	49	44		
Working	45	37		
Not working	0	1		
Missing/can't tell	23	29		

Statistical analyses

Statistical analysis title	Chi-square test of association - week 54

Statistical analysis description:

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

Comparison groups	TFESI v Surgery
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.274 [27]
Method	Chi-squared

Notes:

[27] - The relative risk of not working at 54 weeks cannot be calculate as one of the cell counts for not working is 0.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
An assessment of adverse events was undertaken at each clinical visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Surgery
Reporting group description:	
Any participant who had at least one surgery during the trial are considred in this reporting group.	
Reporting group title	TFESI
Reporting group description:	
Any participant who had at least one TFESI during the trial are considred in this reporting group.	

Serious adverse events	Surgery	TFESI	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 105 (3.81%)	0 / 82 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Surgical procedure repeated			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peroneal nerve palsy			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postoperative wound infection			

subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Surgery	TFESI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 105 (13.33%)	3 / 82 (3.66%)	
Injury, poisoning and procedural complications			
Dural tear			
subjects affected / exposed	4 / 105 (3.81%)	0 / 82 (0.00%)	
occurrences (all)	4	0	
Wound complication			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Pseudomeningocele			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 105 (0.95%)	2 / 82 (2.44%)	
occurrences (all)	1	5	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Radicular pain			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 105 (0.00%)	1 / 82 (1.22%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 105 (0.00%)	1 / 82 (1.22%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 105 (0.95%)	1 / 82 (1.22%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 82 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2015	Change of PI at a site.
08 June 2015	Addition of one new site.
20 August 2015	Change of PI at a site.
13 October 2015	Protocol v4.0 to v5.0: Addition of statistician sign-off and addition of IRMER (Ionising Radiation (Medical Exposure) Regulations).
26 November 2015	Addition of 9 new sites.
08 December 2015	Addition of one new site.
17 February 2016	Change of a site name.
24 February 2016	REC approval date: 23/12/2015. Update of 4 summary of product characteristics documents.
11 May 2016	REC approval date: 18/04/2016. Protocol v5.0 to v6.0: Change of inclusion and exclusion criteria: Duration of symptoms extended from "between 6 weeks and 6 months" to "between 6 weeks and 12 months". Addition of CT scanning for guidance of the TFESI injection. Addition of text clarifying follow-up process and SAE assessment process. Patient information sheet and consent form (PISC) v3.0 to v4.0: Addition of CT scanning for guidance of the TFESI injection.
07 September 2016	Update of 2 summary of product characteristics documents and clarification of reference safety information.
26 January 2017	REC approval date: 02/12/2016. Addition of patient identification sites (PIC).
21 February 2017	Update of 2 summary of product characteristics documents.
10 April 2017	REC approval date: 10/04/2017 Addition of 1 site and creation of trial poster (for use in relevant clinics to raise trial awareness).

15 January 2018	REC approval date: 13/12/2017. MHRA approval date: 04/02/2018. Protocol v6.0 to v7.0: Recruitment target lowered from 200 to 148. Eligibility criteria relating to consent clarified stating written informed consent is needed. Study duration amended from 54 weeks to 54-60 weeks, list of accepted active ingredients and expected maximum doses for use in TFESI group added. Guidance on handling of non-attendance at follow-up visits added. Pharmacovigilance section modified throughout for clarification PISC v5.0 to v6.0: Clarification of data collection, sharing and data use. Health economic letter (how health economic data is collected and used) for patients. Withdrawal statement for trial website. Update of 2 summary of product characteristics documents.
22 August 2018	REC approval date: 20/08/2018 (acknowledged). Update of 4 summary of product characteristics documents.
08 July 2019	MHRA approval date: 03/06/2019. REC approval date: 08/07/2018. Protocol v7.0 to v8.0: Change in lead sponsor contact / signatory. Minor amendments for clarity. Updated withdrawal statement for website. Privacy statement i.e. how data is used and kept secure wording for the trial website.
09 July 2019	HRA approval date: 02/08/2019 MHRA approval date: 23/07/2019. Update of 1 summary of product characteristics document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported