Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix 1: Recruitment & Baseline characteristics

Inclusion exclusion criteria

Patients meeting the following criteria were eligible for inclusion in the trial:

a. Diagnosis of sciatica (lower limb radiculopathy)

b. Sciatica secondary to centro-lateral HLD (nerve compression caused by HLD on MRI with clinical concordance to pain symptoms as assessed by a consultant spinal surgeon; far-lateral discs excluded which precluded midline surgery and where TFESI may be superior)

c. Duration of symptoms between 6 weeks and 12 months. If symptoms were episodic ‘duration of symptoms’ refers to the time since initial incidence of severe symptoms (i.e. the disc prolapse)

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 (Including but not limited to: medication, physiotherapy, modification of daily activities) but this has not provided adequate relief of patient’s pain/symptoms

g. Patient has provided written, informed consent

Patients meeting the following criteria were excluded from the trial:

a. Serious neurological deficit (e.g. foot-drop/possible cauda-equina compression)

b. Previous spinal surgery at the level of the HLD

c. Sciatica episode duration longer than 12 months

d. Age < 16 years

e. Age > 65 years

f. Patient has not attempted any form of conservative treatment

g. Patient with a contraindication for surgery and/or injection

h. Patient known to be pregnant

Table S4: Summary of randomisation by Centre

| Centre Code | Hospital                  | Surgery N | TFESI N | Overall N |
|-------------|---------------------------|-----------|---------|-----------|
| 0006        | James Cook Hospital       | 7         | 7       | 14        |
| 0007        | Addenbrookes Hospital     | 6         | 5       | 11        |
| 0093        | Royal Hallamshire Hospital| 3         | 3       | 6         |
| 0160        | Royal Preston             | 1         | 0       | 1         |
| 0182        | Royal Stoke University Hospital | 1   | 0       | 1         |
| Centre Code | Hospital                                    | Surgery N | TFESI N | Overall N |
|-------------|---------------------------------------------|-----------|---------|-----------|
| 0213        | Nottingham University hospital              | 4         | 4       | 8         |
| 0400        | Salford Royal                              | 4         | 5       | 9         |
| 0428        | The Royal Orthopaedic Hospital, Birmingham  | 3         | 3       | 6         |
| 0492        | Seacroft Leeds                              | 7         | 7       | 14        |
| 0578        | Walton Centre                               | 40        | 40      | 80        |
| 3253        | Solent MSK Services                         | 7         | 6       | 13        |
|             | **Overall**                                 | **83**    | **80**  | **163**   |

**Table S5: Baseline participant demographic characteristics**

| Summary                              | Surgery   | TFESI     | Overall     |
|--------------------------------------|-----------|-----------|-------------|
| Number randomised                    | 83        | 80        | 163         |
| Gender                               |           |           |             |
| N (missing)                          | 83 (0)    | 80 (0)    | 163 (0)     |
| Female                               | 46 (55.4%)| 40 (50.0%)| 86 (52.8%)  |
| Male                                 | 37 (44.6%)| 40 (50.0%)| 77 (47.2%)  |
| Age                                  |           |           |             |
| N (missing)                          | 83 (0)    | 80 (0)    | 163 (0)     |
| Mean (S.D.)                          | 43.5 (9.9)| 41.2 (8.6)| 42.4 (9.3)  |
| Median (Q1-Q3)                       | 42.8 (34.9-50.5)| 41.4 (35.2-47.0)| 42.2 (35.2-48.9)|
| Min-max                              | 23.2 - 65.6 | 23.3 - 59.8 | 23.2 - 65.6 |
| Of reproductive potential (female only) |           |           |             |
| N (missing)                          | 46 (0)    | 40 (0)    | 86 (0)      |
| No                                   | 11 (23.9%)| 5 (12.5%) | 16 (18.6%)  |
| Yes                                  | 35 (76.1%)| 35 (87.5%)| 70 (81.4%)  |
| Weight (Kg)                          |           |           |             |
| N (missing)                          | 75 (8)    | 71 (9)    | 146 (17)    |
| Mean (S.D.)                          | 83.7 (16.8)| 81.4 (20.7)| 82.6 (18.8) |
| Median (Q1-Q3)                       | 82.0 (72.0-95.1)| 77.1 (67.0-94.0)| 79.3 (69.8-94.0)|
| Min-max                              | 54.0 - 134.0 | 51.7 - 154.0 | 51.7 - 154.0 |
| Height (cm)                          |           |           |             |
| N (missing)                          | 76 (7)    | 71 (9)    | 147 (16)    |
| Mean (S.D.)                          | 171.7 (10.7)| 172.6 (9.5)| 172.2 (10.1)|
| Median (Q1-Q3)                       | 170.1 (164.0-180.7)| 173.0 (167.0-180.0)| 171.5 (165.0-180.0)|
| Min-max                              | 147.0 - 197.0 | 150.0 - 192.0 | 147.0 - 197.0 |
| BMI (KG/m²)                          |           |           |             |
| N (missing)                          | 74 (9)    | 68 (12)   | 142 (21)    |
| Number randomised | Summary | Surgery | TFESI | Overall |
|------------------|---------|---------|-------|---------|
| Mean (S.D.)      | 28.2 (5.3) | 27.2 (6.4) | 27.7 (5.9) |
| Median (Q1-Q3)   | 26.9 (24.5-31.3) | 25.6 (22.9-29.4) | 26.4 (24.1-30.7) |
| Min-max          | 18.9 - 44.3 | 17.1 - 47.1 | 17.1 - 47.1 |

Table S6: Baseline details of treatment and effect of sciatica

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Taking Anticoagulant Medication | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| No | 82 (98.8%) | 79 (98.8%) | 161 (98.8%) |
| Yes | 1 (1.2%) | 1 (1.3%) | 2 (1.2%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| No. of weeks of symptoms | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| Mean (S.D.) | 21.5 (10.7) | 21.1 (11.2) | 21.3 (10.9) |
| Median (Q1-Q3) | 17.0 (14.0-28.0) | 18.0 (13.0-27.0) | 18.0 (14.0-28.0) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Previous surgery at disc level | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| No | 82 (98.8%) | 80 (100.0%) | 162 (99.4%) |
| Yes | 1* (1.2%) | 0 (0.0%) | 1 (0.6%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Taken medication for pain and symptoms | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| Yes | 83 (100.0%) | 80 (100.0%) | 163 (100.0%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Modified activity | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| No | 0 (0.0%) | 1 (1.3%) | 1 (0.6%) |
| Yes | 83 (100.0%) | 79 (98.8%) | 162 (99.4%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Attended physiotherapy | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| No | 15 (18.1%) | 16 (20.0%) | 31 (19.0%) |
| Yes | 68 (81.9%) | 64 (80.0%) | 132 (81.0%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Other conservative treatment | |
| N (missing) | 83 (0) | 80 (0) | 163 (0) |
| No | 49 (59.0%) | 43 (53.8%) | 92 (56.4%) |
| Yes | 34 (41.0%) | 37 (46.3%) | 71 (43.6%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Currently employed | |
| N (missing) | 83 (0) | 79 (1) | 162 (1) |
| No | 21 (25.3%) | 13 (16.3%) | 34 (20.9%) |
| Yes | 62 (74.7%) | 66 (82.5%) | 128 (78.5%) |

| Number randomised | Surgery | TFESI | Overall |
|------------------|---------|-------|---------|
| Currently unable to work due to sciatica (of those employed) | |
| N (missing) | 62 (0) | 66 (0) | 128 |
| No | 41 (66.1%) | 34 (51.5%) | 75 (58.6%) |
Note: This patient was not excluded from the primary analysis as the intention to treat principle was followed. This was recorded as a major protocol deviation.

Table S7: Baseline clinical characteristics

|                              | Yes               | 21 (33.9%) | 32 (48.5%) | 53 (41.4%) |
|------------------------------|-------------------|------------|------------|------------|
| Currently taking analgesics/| N (missing)       | 83 (0)     | 80 (0)     | 163        |
| steroids/anticoagulant       | No                | 7 (8.4%)   | 7 (8.8%)   | 14 (8.6%)  |
| medication                   | Yes               | 76 (91.6%) | 73 (91.3%) | 149 (91.4%)|

*Note: Level of disc prolapse was only recorded at treatment visit therefore is not available for participants who did not receive an intervention.

Supplementary Appendix 2: Details of internal pilot

An internal pilot study was included in the trial design. The study targeted two centres to open first to collect 6 months of recruitment data before progressing to a full trial. These centres, Liverpool (Walton Centre) and Manchester (Salford Royal) were identified to cover recruitment of participants within specialty and mixed care settings.

The aim of the internal pilot study was to assess the feasibility of recruitment, and the rates of potential cross-over due to patient preference or treatment failure. The criteria for progression to a full trial were:

- At least 30 patients recruited
- Consent rate of 40% or more
- Fewer than 10% of patients unhappy with allocation and receive the alternative treatment
- Fewer than 50% of patients in the injection group proceed to surgery

*Note: Level of disc prolapse was only recorded at treatment visit therefore is not available for participants who did not receive an intervention.
The internal pilot phase of the trial was reviewed by the IDSMC in September 2015, after 25 participants were recruited from two centres. The committee assessed the recruitment, consent rates, treatment switches and cross-over rates, and recommended that the trial continue with the remaining centres being opened.

**Supplementary Appendix 3: Details of intervention**

**Table S8: Trial interventions received**

| Details | Surgery n=83 | Injection n=80 |
|---------|--------------|----------------|
| n (%)   | n (%)        |                |

*Received randomised treatment initially*

- Single randomised treatment: 65 (78.31)\%
- Repeated randomised treatment: 3 (3.61)\%
- Randomised treatment then the alternative treatment at least once: 3 (3.61)\%

*Received alternative treatment initially*

- Single alternative treatment: 3 (3.61)\%
- Repeated alternative treatment: 1 (1.2)\%
- Alternative treatment then the randomised treatment: 1 (1.2)\%

*Late*/* no treatment*

- No treatment recorded during trial: 4 (4.82)\%
- Late randomised treatment: 0\%
- Late alternative treatment(s): 3 (3.61)\%

*Late refers to treatments that are not received during the initial planned treatment window but are then required at a later time during the study.*

*Red text* denotes patients who crossed arms during the study

**Table S9: Nature of HLD for patients receiving surgery**

| Disc Type | Frequency | % of patients |
|-----------|-----------|---------------|
| Contained | 53        | 71.62         |
| Extruded  | 15        | 20.27         |
| Sequestrated | 6      | 8.11         |
Table S10: Reasons for receiving alternative (non-randomised) treatment at first treatment

| Allocation                  | Details                                           |
|-----------------------------|---------------------------------------------------|
| Surgical Microdiscectomy    | Other anaesthetist decided wasn't safe for surgery|
| Surgical Microdiscectomy    | Patient preference                                |
| Surgical Microdiscectomy    | TFESI                                             |
| Surgical Microdiscectomy    | Other severe sciatic pain down the right leg had resolved. Surgery would be inappropriate. |
| Surgical Microdiscectomy    | Patient preference                                |
| Surgical Microdiscectomy    | patient declined following reflection preferred TFESI |
| Surgical Microdiscectomy    | Patient preference                                |
| TFESI                       | Patient preference                                |
| TFESI                       | Patient preference                                |
| TFESI                       | Surgeon decision                                  |

Table S11: Delay in the initial trial intervention

| Treatment            | Surgery | Injection |
|----------------------|---------|-----------|
|                      | n=83    | n=80      |
| No treatment received* | 7 (8.4) | 7 (8.8)  |
| Within 6 weeks       | 50 (60.2) | 68 (85) |
| Between 6 and 12 weeks | 20 (24.1) | 4 (5) |
| More than 12 weeks   | 6 (7.2) | 1 (1.3)  |

*This refers to the initial planned treatment window only. 6/14 patients who received no treatment at the first planned treatment window subsequently went on to have an intervention later in the study. See Table S8.
### Table S12: Combinations of anaesthetic and steroid used for TFESI

| Anaesthetic | Steroid                      | Total              |
|-------------|------------------------------|--------------------|
|             | Dexamethasone n (% of injections) | Methylprednisolone Acetate n (% of injections) | Trimacinolone Acetonide n (% of injections) |
| Bupivacaine hydrochloride | 3 (3.57)            | 1 (1.19)           | 12 (14.29)           |
| Levobupivacine hydrochloride | 7 (8.33)           | 8 (9.52)           | 51 (60.71)           |
| Lidocaine   | 0                            | 1 (1.19)           | 1 (1.19)            |
| Total       | 10 (11.9)                    | 10 (11.9)          | 64 (76.19)          |
|             | 16 (19.05)                   | 66 (78.57)         | 84                  |

### Table S13: Summary of doses of steroid

| Steroid                        | N  | Mean (SD)       | Min-max |
|--------------------------------|----|----------------|---------|
| Dexamethasone                  | 10 | 7.98 (1.79)     | 6.6 - 11.4 |
| Methylprednisolone Acetate     | 10 | 52 (19.32)      | 40 - 80  |
| Trimacinolone acetonide        | 64 | 40.63 (5)       | 40 - 80  |

### Supplementary Appendix 4: Secondary Outcomes

### Table S14: Summary of baseline scores for longitudinal secondary outcomes

| Outcome     | Summary                  | Surgery | TFESI    | Overall    |
|-------------|--------------------------|---------|----------|------------|
| ODQ         | N (N missing)            | 83 (0)  | 79 (1)   | 162 (1)    |
|             | Mean (S.D.)              | 49.39 (17.81) | 53.74 (19.35) | 51.51 (18.64) |
| VAS leg pain| N (N missing)            | 77 (6)  | 77 (3)   | 154 (9)    |
|             | Mean (S.D.)              | 76.44 (18.70) | 74.58 (22.47) | 75.51 (20.62) |
|          | N (N missing) | 78 (5) | 77 (3) | 155 (8) |
|----------|---------------|--------|--------|---------|
| VAS back pain | Mean (S.D.)   | 51.08 (29.10) | 55.55 (27.01) | 53.30 (28.08) |
| MRM      | N (N missing) | 81 (2) | 79 (1) | 160 (3) |
|          | Mean (S.D.)   | 13.57 (5.40) | 14.78 (5.28) | 14.17 (5.36) |
| COMI     | N (N missing) | 75 (8) | 75 (5) | 150 (13) |
|          | Mean (S.D.)   | 7.13 (1.58) | 7.18 (1.80) | 7.16 (1.69) |
Table S15: Summary of longitudinal secondary outcomes

| Time point | Surgery | TFESI | Overall | Estimated average treatment effect (microdiscectomy vs TFESI) Estimate (95% CI) |
|------------|---------|-------|---------|--------------------------------------------------------------------------------|
|            | N       | Mean (s.d.) | N       | Mean (s.d.) | N       | Mean (s.d.) | Estimate (95% CI) |
| ODQ        | Week 18 | 46  -27.18 (22.31) | 51  -24.29 (18.28) | 97  -25.66 (20.24) | -4.67 (-10.61, 1.28) |
|            | Week 30 | 40  -26.62 (19.12) | 30  -23.25 (17.45) | 70  -25.17 (18.37) |
|            | Week 42 | 40  -31.40 (17.22) | 34  -25.51 (23.74) | 74  -28.69 (20.54) |
|            | Week 54 | 48  -30.38 (17.77) | 42  -31.10 (24.35) | 90  -30.71 (20.97) |
| VAS leg pain | Week 18 | 45  -58.31 (34.51) | 49  -43.55 (32.52) | 94  -50.62 (34.12) |
|            | Week 30 | 38  -54.37 (27.05) | 30  -42.70 (35.27) | 68  -49.22 (31.25) |
|            | Week 42 | 37  -55.81 (31.66) | 33  -47.12 (42.28) | 70  -51.71 (37.03) |
|            | Week 54 | 43  -55.44 (33.57) | 39  -47.08 (33.06) | 82  -51.46 (33.39) | -7.04 (-15.81, 1.73) |
| VAS back pain | Week 18 | 45  -26.02 (32.83) | 49  -23.41 (27.69) | 94  -24.66 (30.12) |
|            | Week 30 | 38  -25.00 (32.04) | 30  -24.33 (31.95) | 68  -24.71 (31.77) |
|            | Week 42 | 37  -20.81 (37.43) | 33  -23.00 (37.29) | 70  -21.84 (37.11) |
|            | Week 54 | 42  -23.07 (34.54) | 39  -22.90 (29.11) | 82  -22.99 (31.84) | -3.01 (-11.29, 5.26) |
| MRM        | Week 18 | 47  -9.09 (6.27)  | 51  -7.73 (5.91)  | 98  -8.38 (6.09)  |
|            | Week 30 | 40  -9.58 (5.60)  | 31  -7.48 (6.68)  | 71  -8.66 (6.14)  |
|            | Week 42 | 39  -9.56 (5.86)  | 34  -8.35 (8.56)  | 73  -9.00 (7.21)  |
|            | Week 54 | 47  -9.74 (6.65)  | 42  -9.24 (6.68)  | 89  -9.51 (6.63)  | -1.82 (-3.67, 0.03) |
| COMI       | Week 18 | 42  -3.93 (2.80)  | 47  -3.05 (2.69)  | 89  -3.46 (2.76)  |
| Week   | 32  | 27  | 59  | 32  | 65  | 76  | 0.77 | -0.77 |
|--------|-----|-----|-----|-----|-----|-----|------|-------|
| 30     | -4.49 (2.44) | -3.33 (2.35) | -3.96 (2.45) | 33  | -4.92 (2.18) | -3.45 (3.14) | -4.20 (2.77) | 39  | -5.02 (2.32) | -3.93 (2.81) | -4.49 (2.61) | -0.77 (-1.58, 0.03) |
Supplementary Appendix 5: Economic Evaluation

Methods
A within-trial economic analysis was performed using patient-level data from the NERVES clinical trial. The analytical approach took the form of a cost-utility analysis using information on health service costs and preference-based health status to calculate an incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained in accordance with the Health Economics Analysis Plan.

The primary analysis followed the approach of the National Institute for Health and Care Excellence (NICE)’s Guide to the Methods of Technology Appraisal 2013 and adopted the perspective of the NHS in England. The economic analysis considered the costs and consequences of each intervention over the 54-week trial period.

A secondary analysis approximating a societal costing perspective additionally considered participant out-of-pocket costs and trial participants’ and their informal carers’ productivity losses arising from time off work.

Resource use
Resource use data were collected from three months (84 days) prior to baseline to the end of the trial at 54 weeks. Resource use categories that might differ between intervention groups were chosen a priori, further differentiated as sciatica-related or non-sciatica-related. Within-trial costs were estimated by measuring healthcare resource use including: (i) microdiscectomy and TFESI procedure, and other hospitalisations including additional treatments, (ii) outpatient and contact with General Practitioners (GPs), physiotherapists and other healthcare professionals, (iii) concomitant medications, (iv) management of adverse events, and (v) participant out-of-pocket costs and productivity losses.

The measurement of resource use required complementary approaches using data collected as part of the NERVES trial as well as routine NHS data. Where multiple sources reported the same type of resource use (e.g. hospital admissions), a hierarchical approach was applied, with priority given to routine HES data, followed by researcher-completed CRFs and lastly participant self-reported questionnaires. The participant cost questionnaire is available on DIRUM.

Unit costs
All resource use was valued in monetary terms (pounds sterling, £/GBP) using appropriate UK unit costs for the cost year 2017/18. Where necessary, adjustments were made for
inflation using the new Health Services (HS) Index using CPI (Health) \(^3\). No discount rate was applied as follow-up was approximately 1 year.

Healthcare resource groups (HRGs) were the main currency of secondary care attendances including the trial interventions, additional treatments, other hospitalisations, outpatient and emergency department visits (Table S11, Table S12, Table S13). NHS National Schedule of Reference Costs 2017/18 \(^4\) were applied as these most closely reflect the actual cost of the provision of care by NHS service providers. HRGs were further sub-categorised according to whether the episode of care took place in the day case, elective or non-elective setting.

The unit costs for all other NHS primary healthcare resource use items were obtained from the Personal Social Services Research Unit (PSSRU) 2018 \(^3\) (Table S14). Visit costs to other healthcare professionals (private physiotherapists, osteopathy and chiropracty, acupuncture) were obtained from publicly available sources \(^5\)-\(^8\).

The costs of concomitant medications (Table S15) were obtained from Prescription Cost Analysis data \(^9\) supplemented by the British National Formulary \(^10\) whilst over the counter medication costs were obtained from published retail pharmacy sources \(^11\).

Lost productivity was based on participant-reported lost earnings. In scenario analyses, Office of National Statistics (ONS) Annual Survey of Hours and Earnings (ASHE) median wage values were applied based on full-time employment \(^12, 13\) (Table S16). Other out-of-pocket participant costs associated with public transport to attend medical appointments were based on participant self-report, and if travel was undertaken in a private car, a cost per mile of £0.68, including vehicle running costs, was applied \(^14, 15\).

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**Table S16: Unit costs of Admitted Patient Care.** The HRGs listed represent those reported \(>2\%\) by frequency of all HRGs\(^{a,b}\).

| Intervention       | HRG code | Description                                      | Attendance | Cost per episode |
|--------------------|----------|--------------------------------------------------|------------|-----------------|
| Microdiscectomy    | HC64C    | Intermediate extradural spinal procedures with CC Score 0-1\(^c\) | Day case   | £1,971           |
|                    | HC64B    | Intermediate extradural spinal procedures with CC Score 2-3 | Elective   | £4,782           |
|                    | HC63C    | Major extradural spinal procedures with CC Score 0-1 | Elective   | £4,858           |
|                    |          |                                                  | Non-elective | £5,696           |
| TFESI              | AB20Z    | Epidural under image control for pain management  | Day case   | £711             |
| Hospitalisation    | HC27N    | Degenerative spinal                              | Non-elective | £1,827           |
without surgical intervention

Conditions without Interventions, with CC Score 0-2

Other AA26H Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2

WH50B Procedure Not Carried Out, for Other or Unspecified Reasons

Daycase Non-elective £523 £1,490

Daycase Elective £338 £599

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a NHS National Schedule of Reference Costs 2017/18
b Medication costs associated with delivery of interventions, including TFESI steroid and local anaesthetic assumed to be included in the HRG cost
c CC Score is a measure of severity and complexity, with higher scores reflecting increased patient complications or comorbidities

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Table S17: Unit costs of outpatient attendances. The HRGs listed represent those reported >2% by frequency by treatment area⁴.

| Treatment area          | HRG Code | Description                                      | Consultant led (CL) or non-consultant led (NCL) | Cost per episode |
|-------------------------|----------|--------------------------------------------------|-----------------------------------------------|------------------|
| Anaesthetics            | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | CL                                            | £124             |
| Neurosurgery            | WF01B    | Non-Admitted Face-to-Face Attendance, First      | CL                                            | £257             |
|                         | WF01B    | Non-Admitted Face-to-Face Attendance, First      | NCL                                           | £153             |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | CL                                            | £179             |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | NCL                                           | £174             |
| Pain Management         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | CL                                            | £147             |
| Physiotherapy           | WF01B    | Non-Admitted Face-to-Face Attendance, First      | NCL                                           | £61              |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | NCL, CL                                       | £52              |
| Spinal Surgery Service  | WF01B    | Non-Admitted Face-to-Face Attendance, First      | CL                                            | £163             |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | CL                                            | £135             |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | NCL                                           | £81              |
| Trauma & Orthopaedics   | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | CL                                            | £119             |
|                         | WF01A    | Non-Admitted Face-to-Face Attendance, Follow-up  | NCL                                           | £93              |

⁴ NHS National Schedule of Reference Costs 2017/18
### Table S18: Unit costs of Emergency Department visits

| Admission | HRG code | Description | Cost per episode<sup>a</sup> |
|-----------|----------|-------------|-------------------------------|
| Emergency Medicine | VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z, VB10Z, VB11Z, VB99Z | Weighted mean cost by proportion of attendances by code to the Emergency Department | £160.32 |

<sup>a</sup>NHS National Schedule of Reference Costs 2017/18<sup>4</sup>

### Table S19: Unit costs of healthcare professional attendances<sup>a</sup>

| Healthcare professional attendance | Cost per episode<sup>*</sup> | Costing perspective | Source |
|-----------------------------------|-----------------------------|---------------------|--------|
| GP surgery                        | £31.43                      | NHS                 | PSSRU 2018<sup>3</sup> |
| GP out-of-hours surgery           | £109.59                     | NHS                 | PSSRU 2018                |
| GP home visit (call-out)          | £102.10                     | NHS                 | PSSRU 2013<sup>16</sup>, PSSRU 2018 |
| NHS physiotherapist               | £46.00                      | NHS                 | PSSRU 2018                |
| Acupuncture                       | £43.10                      | Wider perspective   | NHS 2016<sup>1</sup>      |
| Osteopath / chiropractor          | £48.75                      | Wider perspective   | NHS 2018<sup>6</sup>, NHS, 2017<sup>7</sup> |
| Private physiotherapist           | £50.70                      | Wider perspective   | Capital Physio 2016<sup>5</sup> |

<sup>a</sup>All costs not reported in base-case year prices are inflated to 2017/2018 values using the new Health Services (HS) Index using CPI (Health)<sup>3</sup>.

### Table S20: Unit costs of the top 10 most commonly prescribed medications

| Medication  | Formulation                     | Cost per unit<sup>a</sup> |
|-------------|--------------------------------|-----------------------------|
| Gabapentin  | 100mg capsule                   | £0.02                       |
|             | 300mg capsule                   | £0.14                       |
|             | 400mg capsule                   | £0.03                       |
|             | 600mg tablet                    | £0.06                       |
|             | 800mg tablet                    | £0.30                       |
|             | 50mg/ml sugar free solution     | £0.46                       |
|             | 250mg/5ml oral suspension       | £0.01                       |
|             | 500mg tablet                    | £0.02                       |
| Paracetamol | 250mg tablet                    | £0.03                       |
| Naproxen    | 250mg tablet                    | £0.04                       |
|             | 500mg tablet                    |                             |
| Morphine    | 10mg tablet Sevredol®           | £0.09                       |
|             | 10mg tablet MST Continus®       | £0.09                       |
|             | 10mg capsule Zomorph®           | £0.06                       |
|             | 30mg capsule Zomorph®           | £0.14                       |
| Drug                  | Formulation                  | Price  |
|----------------------|------------------------------|--------|
| 100mg capsule Zomorph® |                              | £0.36  |
| 10mg/5ml oral solution Oromorph® |                        | £0.02  |
| Tramadol             | 50mg capsule                 | £0.03  |
|                      | 50mg modified release capsule | £0.12  |
|                      | 100mg modified release capsule| £0.24  |
|                      | 50mg/ml 2ml injection        | £1.12  |
| Co-codamol           | 8mg/500mg tablet             | £0.03  |
|                      | 15mg/500mg tablet            | £0.05  |
|                      | 30mg/500mg tablet            | £0.04  |
|                      | 30mg/500mg tablet Zapain®    | £0.03  |
| Ibuprofen            | 200mg tablet                 | £0.03  |
|                      | 400mg tablet                 | £0.03  |
|                      | 256mg tablet Nurofen Express®| £0.14  |
|                      | 200mg long lasting capsules Boots® | £0.21  |
|                      | Gel 5%                       | £0.05  |
|                      | Gel 5% Nurofen®              | £0.09  |
|                      | Gel 10%                      | £0.05  |
| Amitriptyline        | 10mg tablet                  | £0.03  |
|                      | 20mg tablet                  | £0.05  |
|                      | 25mg tablet                  | £0.03  |
|                      | 35mg tablet                  | £0.06  |
|                      | 50mg tablet                  | £0.09  |
|                      | 10mg/5ml solution            | £0.74  |
| Pregabalin           | 75mg capsule Lyrica®         | £1.15  |
|                      | 150mg capsule Lyrica®        | £1.15  |
|                      | 300mg capsule Lyrica®        | £1.15  |
|                      | 50mg capsule                 | £0.14  |
|                      | 75mg capsule                 | £0.10  |
|                      | 100mg capsule                | £0.12  |
|                      | 150mg capsule                | £0.15  |
|                      | 200mg capsule                | £0.15  |
|                      | 300mg capsule                | £0.18  |
| Codeine Phosphate    | 15mg tablet                  | £0.03  |
|                      | 30mg tablet                  | £0.04  |
|                      | 60mg tablet                  | £0.05  |

* PCA – Prescription Cost Analysis, September 2017 or published retail pharmacy prices. A unit refers to a single tablet or capsule, or per ml or per mg for liquids and topical gels.
### Table S21: Net daily earnings (alternative productivity losses)

| Category | Net daily earnings | By hospital Local Authority Area (LAA) |
|----------|-------------------|----------------------------------------|
|          | Male\(^a\)       | Female\(^a\)                           |                                      |
| Age      |                   |                                        |                                      |
| 22-29    | £75.16            | £70.18                                 |                                      |
| 30-39    | £93.64            | £85.82                                 |                                      |
| 40-49    | £102.63           | £84.27                                 |                                      |
| 50-59    | £100.40           | £79.35                                 |                                      |
| 60+      | £87.87            | £71.05                                 |                                      |
| Hospital LAA |                |                                        |                                      |
| Middlesbrough | £79.39      |                                        |                                      |
| Cambridge  | £92.02            |                                        |                                      |
| Sheffield  | £81.85            |                                        |                                      |
| Preston    | £79.94            |                                        |                                      |
| Stoke-on-Trent | £76.69   |                                        |                                      |
| Nottingham | £77.52            |                                        |                                      |
| Salford    | £81.20            |                                        |                                      |
| Birmingham | £84.95            |                                        |                                      |
| Leeds      | £84.13            |                                        |                                      |
| Liverpool  | £82.41            |                                        |                                      |
| Southampton| £88.68            |                                        |                                      |

\(^a\) Calculated from ONS 2017. Annual Survey of Hours and Earnings 2017, Table 6.1a. Weekly pay – Gross (£) – For full-time employee jobs: United Kingdom, 2017. \(^b\) Calculated from ONS 2017, Annual Survey of Hours and Earnings, 2017 provisional and 2016 revised results. 9. Regional Earnings, Figure 13. Median full-time gross weekly earnings by place of work, Great Britain, April 2017.

### Cost analysis

For completeness, all resource use was measured and costed irrespective of reason but, to allow for scenario analysis, was categorised as sciatica-related or not as reported in the CRFs or patient questionnaire. Medications were categorised based on reason for prescription whilst HES data were categorised by reason for admission, according to HRG code. The trial design also allowed for further treatment at the discretion of the clinician in the event of incomplete symptom resolution, and costs for subsequent treatments within the trial period were collected via the HES dataset and included in the analysis.

To cost secondary care episodes, HES data were sourced from NHS Digital in the form of a series of routinely available codes and dates, including participant diagnoses, admission
dates, discharge dates and then converted into HRG codes using the NHS Digital HRG4+ 2018/19 Payment Grouper 17. Treatment costs were applied on the basis of treatment received, with only the costs of treatments received being accrued. Visits to Emergency Departments were costed based on participant self-report and a mean cost per visit was applied according to the National Schedule. To allow for follow-up visits that occurred out of the trial window, all protocol-related visits that were scheduled identically in both intervention groups were included, but all other visits outside of the 54-week trial were excluded.

The resource use questionnaire collected participant-reported resource use for the preceding three months (or six weeks at treatment visit). Quantities of resource use for primary care services, including visits to the GP (surgery, out-of-hours or home visit), physiotherapist, acupuncturist, chiropractor and osteopath and any other healthcare professional were taken from participant responses and multiplied by unit costs to estimate total costs. Since the base-case analysis took the NHS perspective, all visits to the GP were included, as were NHS physiotherapist visits, assumed on the basis of a participant-reported out-of-pocket cost of less than £20, which was attributed to travel costs. Physiotherapy visits with costs greater than £20 were assumed to be private physiotherapy visits and were included in the secondary analysis adopting a wider perspective as were the costs of visits to the acupuncturist, chiropractor, osteopath and any other healthcare professionals, and any over the counter medications on the basis that the NHS does not routinely fund these treatments. Questionnaires not completed within the pre-defined visit windows were considered protocol deviations but nonetheless were included in the analysis using appropriate time-based adjustments.

Prescribed medication costs were calculated based on CRF-recorded medication usage at baseline, treatment and follow-up visits weeks 18 and 54. All tablets, capsules, oral liquids, sprays and inhalers were costed on a unit dose basis, and creams and gels were assumed to be supplied on a one pack per month basis. Medications administered on an “as needed” basis were costed assuming administration based on 50% of the standard dose recommended in the BNF.

Out-of-pocket travel costs and participant or carer productivity losses were also obtained from the resource use questionnaire. Participants were asked to report both the number of days off work and lost earnings. Where the number of days off work was reported, but lost earnings values were missing, it was assumed that there were no lost earnings, i.e. participants received sick pay.

Health outcome measures

Health benefits were measured in QALYs, using the EQ-5D-5L descriptive measure of health status administered to participants at baseline, and weeks 18, 30, 42 and 54. In the base-case analysis, the EQ-5D-5L to EQ-5D-3L crosswalk valuation set, the current NICE preferred value...
set \(1, 18, 19\), was employed to generate utility scores. QALYs were calculated according to the ‘area under the curve’ approach \(20\), assuming linear changes in utility values over time for each participant’s longitudinal measures of utility.

**Missing data**

Data for hospital admissions, outpatient care and concomitant medications were considered to be complete but the resource use and EQ-5D questionnaires were subject to missing data. Missing utility scores at baseline, 18 weeks or 54 weeks were imputed as were missing resource use costs at any missing time point. Imputation used multiple imputation via chained equations (MICE) and the method of predictive mean matching implemented in the ‘mice’ package in the R statistical computing environment, version 3.6.1 \(21\). This assumes data was Missing at Random \(22\). For the base-case analysis and in all scenario analyses a total of ten complete imputed datasets were generated \(23\). Where bootstrapping was used, the process of multiple imputation, statistical analysis and pooling was performed on each bootstrap replicate.

**Approach to analysis**

The study collected participants’ use of healthcare resources for the three months prior to randomisation and EQ-5D responses at randomisation. This was to allow for adjustments of any imbalance in costs and utilities observed between treatment groups at baseline and for correlation between baseline and follow-up responses. Total costs and utilities at baseline were correlated with follow-up costs and QALYs. Therefore, regression analyses were conducted in order to quantify the impact of treatment allocation on follow-up costs and QALYs whilst controlling for baseline costs and utilities, respectively. Regression models were estimated using each of the ten imputed datasets and coefficients were averaged to obtain point estimates as per Rubin’s rules \(24\). The analysis was performed using the R statistical computing environment, version 3.6.1 \(21\). R scripts used to perform the final stage of the analysis including bootstrap, multiple imputation and statistical modelling can be found at https://github.com/dh-mcmanus/NERVES.

Participant QALYs were modelled using multiple linear regression, with treatment allocation and baseline utilities (continuous) as independent variables. Additional models were estimated including combinations of the other potential independent variables (including treatment site, participant gender, participant age group and weeks of leg pain symptoms), but these were ruled out based on F or t-tests for nested model comparisons and inspection of residual plots. The relationship between baseline utilities and subsequent QALYs was approximately linear and thus no additional terms or transformations were included.

Participant follow-up costs were modelled using a generalised linear model with a log-link function and gamma probability distribution, with treatment allocation and baseline costs (continuous) as independent variables. Identity link, or log-link and Gaussian probability distribution were considered as alternatives. These were ruled out based on comparisons of
the Akaike Information Criterion (AIC) statistic and inspection of residual plots. In both models, trial centre was tested as a random effect coefficient but not included since the estimated variance was close to zero. Beyond consideration of alternative link functions, we did not attempt to include more terms involving baseline costs to allow for more complex functional relationships.

**Incremental Cost-Effectiveness Ratio**

The cost-effectiveness of microdiscectomy compared to TFESI was assessed by its incremental cost-effectiveness ratio (ICER) calculated according to the formula:

\[
\text{Incremental cost-effectiveness ratio (ICER)} = \frac{\Delta \text{Costs}}{\Delta \text{QALY}}
\]

Uncertainties in QALYs, the incremental results and resulting cost-effectiveness metrics were evaluated using a non-parametric bootstrap of 10,000 replicates of the patient-level data and uncertainty in the ICER was represented graphically on the cost-effectiveness plane and cost-effectiveness acceptability curve 25.

**Base-case analysis**

The base-case analysis, over the 54-week trial period, was based on the imputed data set to account for missing data and subject to the regression analysis (Table 17).

**Table S22: Base-case analysis key methods**

| Item                  | Description and approach                                         |
|-----------------------|-------------------------------------------------------------------|
| Comparator            | Microdiscectomy vs TFESI                                          |
| Population            | NERVES trial participants diagnosed with sciatica secondary to PID|
| Analysis approach     | ITT, but excluding withdrawn participants (N=157)                |
| Model type and description | Within trial cost-effectiveness analysis, imputed dataset, subject to regression |
| Cost-effectiveness metrics | Non-parametric bootstrap, mean and 95% CI                      |
| Perspective           | NHS                                                               |
| Time horizon          | 54 weeks                                                          |
| Discount rate         | Not applicable, trial limited to ≈ 1 year                        |
| Utility values        | EQ-5D-5L mapped using 3L crosswalk value set                     |
| Health outcome        | QALYs measured from utility values                                |
| Adverse effects       | Costs only, associated with secondary care admissions             |
| Resource use          |                                                                  |
| Secondary care        | Hospital Episode Statistics                                       |
Scenario analyses were conducted to assess the impact of considering alternative perspectives, inputs and costs on the ICER. These were: i) a wider approximating to a societal perspective, which included participant costs associated with time off work and other out-of-pocket costs comprising of self-funded healthcare practitioner visits, medical appointment travel costs and over the counter medications (SA1); ii) a complete case analysis, which included only participants presenting complete cost data for all cost variables at all time points and outcome data at baseline, week 18 and week 54 (SA2); iii) employing alternative EQ-5D scoring methods (SA3,SA4)\(^26\); iv) an alternative costing approach for the resource use questionnaire, based on last completed questionnaire date rather than the previous three months (SA5); v) considering sciatica-related costs only (SA6); vi) alternative frequencies of administered ‘when needed’ medication (SA7,SA8); and vi) alternative costing approaches for societal costs associated with productivity losses (SA9,SA10,SA11,SA12).

Results

Data completeness

The analysis was based on the intention-to-treat (ITT) population; 163 participants were recruited to the trial but six participants withdrew early on and were excluded from the cost-effectiveness analysis since no outcome data nor HES data was available. Data from 157 participants was therefore included in the economic evaluation (80 in the microdiscectomy group and 77 in the TFESI group). Resource use and EQ-5D-5L questionnaires were not completed by all participants. Completion rates were best at baseline, treatment and week 18 visits, but high levels of missingness were observed for the week 30 and week 42 postal questionnaires (Table S18).
| Item                          | Baseline | Treatment | Number (%) of Missing Observations |
|------------------------------|----------|-----------|------------------------------------|
|                              | Surgery  | TFESI     | Surgery  | TFESI | Surgery  | TFESI | Surgery  | TFESI | Surgery  | TFESI | Surgery  | TFESI |
|                              |          |           |          |       |          |       |          |       |          |       |          |       |
| *Utility scores*             |          |           |          |       |          |       |          |       |          |       |          |       |
| EQ-5D-5L                     | 4 (5)    | 2 (2.6)   | - (-)    | - (-) | 12 (15)  | 14 (18.2) | 29 (36.3) | 34 (44.2) | 29 (36.3) | 33 (42.9) | 16 (20) | 20 (26) |
|                              |          |           |          |       |          |       |          |       |          |       |          |       |
| *Resource use*               |          |           |          |       |          |       |          |       |          |       |          |       |
| GP                           |          |           |          |       |          |       |          |       |          |       |          |       |
|                              | 16 (20)  | 14 (18.2) | 15 (18.8) | 10 (13)| 18 (22.5) | 20 (26) | 33 (41.2) | 38 (49.4) | 35 (43.8) | 41 (53.2) | 25 (31.2) | 26 (33.8) |
| Physiotherapy                | 3 (3.8)  | 3 (3.9)   | 12 (15)  | 7 (9.1)| 11 (13.8) | 11 (14.3) | 29 (36.2) | 34 (44.2) | 30 (37.5) | 33 (42.9) | 17 (21.2) | 18 (23.4) |
| Emergency Department         | 4 (5)    | 4 (5.2)   | 14 (17.5) | 7 (9.1)| 12 (15)  | 12 (15.6) | 29 (36.2) | 33 (42.9) | 29 (36.2) | 33 (42.9) | 18 (22.5) | 18 (23.4) |
| OTC medications              | 3 (3.8)  | 3 (3.9)   | 13 (16.2) | 7 (9.1)| 12 (15)  | 11 (14.3) | 30 (37.5) | 33 (42.9) | 31 (38.8) | 32 (41.6) | 17 (21.2) | 19 (24.7) |
| Public transport             | 4 (5)    | 3 (3.9)   | 12 (15)  | 7 (9.1)| 11 (13.8) | 12 (15.6) | 29 (36.2) | 33 (42.9) | 29 (36.2) | 34 (44.2) | 16 (20)  | 18 (23.4) |
| Private car                  | 4 (5)    | 3 (3.9)   | 12 (15)  | 8 (10.4)| 12 (15)  | 12 (15.6) | 30 (37.5) | 35 (45.5) | 29 (36.2) | 35 (45.5) | 18 (22.5) | 19 (24.7) |
| Lost productivity – participant | 4 (5)    | 3 (3.9)   | 12 (15)  | 7 (9.1)| 11 (13.8) | 12 (15.6) | 30 (37.5) | 34 (44.2) | 30 (37.5) | 32 (41.6) | 16 (20)  | 18 (23.4) |
| Lost productivity – carer    | 3 (3.8)  | 2 (2.6)   | 12 (15)  | 7 (9.1)| 11 (13.8) | 11 (14.3) | 29 (36.2) | 34 (44.2) | 29 (36.2) | 32 (41.6) | 16 (20)  | 18 (23.4) |

OTC: Over The Counter

*a* Considered a missing item when it was not possible to calculate a cost because frequency of visits and/or visit cost was missing.
Resource use and cost analysis

Observed participant use of healthcare resources were comparable at baseline in both intervention groups for the three months prior to randomisation (Table S19). Table S20 and Table present the observed disaggregated healthcare resource use and costs, respectively, over 54-week trial period. During the 54-week trial period, our data indicated that admitted patient care accounted for the majority of costs followed by outpatient attendances and concomitant medications. Mean observed total NHS costs were higher for microdiscectomy at £6,683 (95% CI £5,632, £8,074) compared to TFESI £4,422 (95% CI £3,682, £5,291) and the incremental analysis yielded a difference in mean of £2,261 (95% CI £706, £3,589). The main cost difference between groups was for admitted patient care, with microdiscectomy costing £1,926 (95% CI £467, £3,128) more than TFESI. The cost of outpatient attendances also differed between groups, with costs for microdiscectomy being £237 (95% CI £50, £414) greater than TFESI, reflecting higher rates of neurosurgery and physiotherapy outpatient visits for the surgical group. Total combined NHS and societal costs were higher for the microdiscectomy group (microdiscectomy £7,561 (95%CI £6,465, £8,985), TFESI £5,729 (95%CI £4,596, £7,006) difference in mean £1,832, (95% CI £53, £3,555)) but no difference in participant out of pocket costs was observed (difference in mean £429, (95%CI -£1,140, £403)) (Table S21).

Table S24: Observed baseline costs in the three months prior to randomisationa

| Item                      | Treatment group, mean, (£) (95% CI) | Difference in mean (£), (95% CI) |
|---------------------------|-------------------------------------|---------------------------------|
|                           | Microdiscectomy                      | TFESI                           |                                  |
|                           | Sciatica-related costs               | Total costs                     | Sciatica-related costs           | Total costs | Sciatica-related costs | Total costs |
| Total NHS & Societal      | 1,707 (1,246, 2,299)                | 1,790 (1,326, 2,358)            | 1,596 (1,922, 2,015)            | 1,684 (1,280, 2,155) | 111 (-583, 795)       | 106 (-609, 783) |
|                           | 807 (602, 1,032)                    | 882 (673, 1,135)                | 866 (610, 1,174)                | 950 (677, 1,291)    | -59 (-410, 315)       | -68 (-422, 334)  |
| Admitted Patient Care     | 327 (141, 525)                      | 353 (171, 552)                 | 384 (159, 660)                 | 422 (182, 699)      | -56 (-357, 282)       | -69 (-376, 276)  |
| Outpatient                | 185 (150, 221)                      | 208 (169, 252)                 | 231 (172, 311)                 | 251 (187, 330)      | -47 (-127, 42)        | -43 (-125, 51)   |
| Concomitant medications   | 51 (38, 69)                         | 63 (48, 83)                    | 34 (24, 47)                    | 45 (32, 60)         | 17 (-3, 36)           | 19 (-4, 41)      |
| GP                        | 152 (125, 180)                      | 169 (140, 202)                 | 142 (108, 183)                 | 153 (118, 195)      | 10 (-35, 57)          | 16 (-31, 64)     |
| Physiotherapy | 59  | 59  | 52  | 52  | 7   | 7   |
|---------------|-----|-----|-----|-----|-----|-----|
|               | (37, 84) | (37, 84) | (24, 84) | (26, 84) | (-30, 47) | (-30, 46) |
| Emergency     | 89  | 92  | 80  | 89  | 9   | 4   |
| Department    | (59, 124) | (62, 125) | (57, 108) | (59, 122) | (-33, 51) | (-40, 50) |
| Societal      | 900 | 907 | 730 | 734 | 170 | 174 |
|               | (495, 1,423) | (497, 1,427) | (473, 1,031) | (480, 1,051) | (-433, 699) | (-433, 697) |
| Physiotherapy & other HP visits | 69  | 69  | 93  | 93  | -24 | -24 |
|               | (35, 112) | (35, 111) | (53, 140) | (55, 134) | (-81, 31) | (-82, 32) |
| OTC medication | 28  | 28  | 21  | 22  | 7   | 6   |
|               | (19, 37) | (20, 38) | (13, 31) | (13, 31) | (-6, 19) | (-6, 19) |
| Lost productivity, participant & carer | 804 | 809 | 611 | 614 | 193 | 196 |
|               | (398, 1,363) | (392, 1,388) | (353, 895) | (349, 913) | (-407, 718) | (-401, 711) |
| Medical appointment transport | 45  | 46  | 34  | 35  | 10  | 11  |
|               | (24, 76) | (25, 75) | (24, 47) | (24, 49) | (-23, 35) | (-23, 37) |

HP: Healthcare professionals; OTC: Over the counter;
*Admitted patient care, outpatient and concomitant medications data considered complete. Resource Use Questionnaire missing values excluded to reflect participants with missing data in Table S18. Mean values based on the number of patients reporting each item.

Table S25: Observed disaggregated healthcare resource use, HRGs recorded >2% by frequency over 54 weeks from randomisation*

| Admitted Patient Care HRGb | Microdisectomy | TFESI | Difference (95% CI) |
|----------------------------|----------------|-------|---------------------|
| HC64C, Intermediate Extradural Spinal Procedures with CC Score 0-1 | 66.2 | 28.8 | 37.4 (17.8, 57.1) |
| HC64B, Intermediate Extradural Spinal Procedures with CC Score 2-3 | - | - | -2.6 (-7.5, -0.1) |
| HC63C, Major Extradural Spinal Procedures with CC Score 0-1 | - | - | 9.4 (2.0, 19.2) |
| AB20Z, Epidural Under Image Control for Pain Management | 9.6 | 86.3 | -76.7 (-91.4, -64.4) |
| HC27N, Degenerative Spinal Conditions without Interventions, with CC Score 0-2 | - | - | -3.8 (-8.7, -3.8) |
| AA26H, Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2 | - | - | -7.6 (-12.5, -7.6) |
WH50B, Procedure Not Carried Out, for Other or Unspecified Reasons  

|                      | -   | -   | 4.8 (4.8, 9.7) |
|----------------------|-----|-----|---------------|

Outpatient HRG

| Service                  | Mean | Standard Deviation | 95% CI          |
|--------------------------|------|--------------------|-----------------|
| Neurosurgery             | 306.9| 200.1              | 107 (60, 153)   |
| Physiotherapy            | 158.9| 53.8               | 105 (78, 132)   |
| Anaesthetics             | 110.7| 147.6              | -37 (-71, -2)   |
| Pain Management          | 45.7 | 68.8               | -23 (-45, -1)   |
| Spinal Surgery Service   | 60.2 | 56.3               | 4 (-21, 26)     |

GP and healthcare professional visits

| Service          | Mean | Standard Deviation | 95% CI          |
|------------------|------|--------------------|-----------------|
| GP               | 296.1| 356.4              | -60.3 (-242.9, 121.9) |
| Physiotherapy    | 72.2 | 91.3               | -19.1 (-104.9, 71.2) |
| Acupuncture      | 16.9 | 6.3                | 10.6 (-17.1, 31.2) |
| Chiropractor/Osteopath | 4.8 | 2.5              | 2.3 (-6.2, 8.5)  |
| Other            | 32.5 | 16.3               | 16.2 (-25.3, 50.4) |
| Emergency Department | 19.3| 26.3              | -7.0 (-26.8, 12.9) |

Lost productivity

|                         | Mean | Standard Deviation | 95% CI          |
|-------------------------|------|--------------------|-----------------|
| Days off work - participant | 1,999| 2,146             | -147 (-1,615, 1,353) |
| Days off work - carer   | 229  | 144               | 84 (-126, 265)  |

CC, Complication and comorbidity

*Admitted patient care and outpatient data considered complete but follow up was variable in duration and trimmed to 54 weeks where it exceeded 54 weeks. No adjustment was made to patients with < 54 week data, assumed complete. Resource Use Questionnaire missing values excluded to reflect participants with missing data in Table S23.

*Redacted text: to comply with the HES Analysis Guide 27 (as per Data Sharing Agreement with NHS Digital) HRGs observed seven times or less in either of the treatment groups are not reported.

**Table S26: Observed disaggregated and total 54-week costs from randomisation**

| Item                          | Treatment group, mean, (£) (95% CI) |
|-------------------------------|------------------------------------|
|                               | Microdiscectomy | TFESI | Difference in mean, (£) (95% CI) |
|                               | Sciatica | Total | Sciatica | Total | Sciatica | Total |
| Total NHS & Societal          | 6,522    | 7,561 | 5,171    | 5,729 | 1,351    | 1,832 |
|                               | (5,839, 7,292) | (6,465, 8,985) | (4,193, 6,213) | (4,596, 7,006) | (127, 2,573) | (53, 3,555) |
| NHS                           | 5,780    | 6,683 | 4,150    | 4,422 | 1,630    | 2,261 |
|                               | (5,191, 6,420) | (5,632, 8,074) | (3,440, 4,928) | (3,682, 5,291) | (674, 2,580) | (706, 3,589) |
| Admitted Patient Care         | 4,523    | 5,168 | 3,110    | 3,242 | 1,413    | 1,926 |
|                               | (3,975, 5,144) | (4,271, 6,475) | (2,452, 3,731) | (2,617, 3,924) | (560, 2,275) | (467, 3,128) |
| Outpatient                    | 1,066    | 1,186 | 885      | 949   | 181      | 237  |
|                               | (953, 1,181) | (1,045, 1,327) | (792, 977) | (842, 1,066) | (28, 325) | (50, 414) |
| Concomitant medications       | 155      | 262   | 126      | 183   | 29       | 78   |
|                               | (155, 262) | (126, 183) | (29, 78) | (155, 262) | (126, 183) | (29, 78) |
| GP          | (107, 219) | (168, 385) | (80, 181) | (125, 252) | (-49, 105) | (-62, 199) |
|-------------|------------|------------|-----------|------------|------------|------------|
|             | 44         | 93         | 49        | 103        | -5         | -10        |
|             | (23, 72)   | (52, 137)  | (18, 90)  | (56, 166)  | (-45, 39)  | (-77, 62)  |
| Physiotherapy | 38       | 38         | 18        | 18         | 19         | 19         |
|             | (3, 84)    | (3, 88)    | (0, 44)   | (0, 44)    | (-37, 62)  | (-35, 62)  |
| Emergency Department | 15 | 50        | 45        | 71         | -30        | -20        |
|             | (0, 40)    | (10, 100)  | (13, 90)  | (26, 128)  | (-74, 20)  | (-94, 50)  |
| Societal    | 742        | 878        | 1,021     | 1,307      | -279       | -429       |
|             | (457, 1,124) | (538, 1,204) | (516, 1,659) | (708, 2,092) | (-884, 407) | (-1,140, 403) |
| Physiotherapy & other HP visits | 10 | 10        | 24        | 24         | -14        | -14        |
|             | (2, 20)    | (2, 20)    | (7, 47)   | (7, 47)    | (-34, 10)  | (-34, 10)  |
| OTC         | 27         | 33         | 20        | 25         | 7          | 8          |
|             | (18, 39)   | (22, 45)   | (13, 30)  | (16, 35)   | (-7, 21)   | (-7, 23)   |
| Lost        | 660        | 781        | 939       | 1,128      | -279       | -347       |
| productivity, participant & carer | (373, 1,033) | (455, 1,160) | (476, 1,561) | (557, 1,850) | (-887, 425) | (-1,037, 510) |
| Medical appointment transport | 45 | 54        | 38        | 130        | 7          | -76        |
|             | (30, 62)   | (39, 72)   | (24, 57)  | (29, 319)  | (-16, 31)  | (-184, 123) |

HP: Healthcare professionals; OTC: Over the counter;
*Admitted patient care, outpatient and concomitant medications data considered complete. Resource Use Questionnaire missing values excluded to reflect participants with missing data in Table S18.

Utility and quality-adjusted life year outcomes

Mean utility scores were comparable between participant groups at baseline (Figure S1, Table S22), and similarly comparable QALYs were observed in patients who completed the questionnaires at baseline, week 18 and 54 (0.654 QALYs for microdiscectomy, 0.591 QALYs for TFESI, difference in mean 0.062 (95% CI -0.033, 0.155). The 5L value sets and VAS results exhibited a tendency to generate higher utility scores than the 3L value set, but showed minimal differences in QALY gains over the 54 week trial period that were also not statistically different.
Figure S1: Utility scores by visit using 3L crosswalk value set, observed data

Table S27: Health outcomes for participants with observations at baseline, week 18 and week 54, adjusted for visit time deviations

| Analysis          | Health Outcome | Microdiscectomy Mean (95% CI) | TFESI Mean (95% CI) | Difference in mean (95% CI) |
|-------------------|----------------|------------------------------|--------------------|----------------------------|
| EQ-5D-3L value set | Baseline utility | 0.328 (0.259, 0.392)          | 0.276 (0.188, 0.366) | 0.052 (-0.060, 0.157)      |
|                   | 54-week utility | 0.718 (0.649, 0.784)          | 0.659 (0.573, 0.739) | 0.059 (-0.051, 0.165)      |
|                   | QALYs over 54 weeks | 0.654 (0.588, 0.709)          | 0.591 (0.518, 0.658) | 0.062 (-0.033, 0.155)      |
| EQ-5D-5L value set | Baseline utility | 0.443 (0.377, 0.513)          | 0.409 (0.322, 0.486) | 0.034 (-0.071, 0.137)      |
|                   | 54-week utility | 0.794 (0.728, 0.851)          | 0.737 (0.660, 0.807) | 0.057 (-0.041, 0.157)      |
**Cost-effectiveness analysis results**

**Base-case analysis**

In the base-case analysis, following imputation, regression analysis and non-parametric bootstrapping, microdiscectomy in relation to TFESI fell in the North East quadrant of the cost-effectiveness plane (Figure S2), indicating microdiscectomy to be more costly, but with greater (but not statistically different) quality of life benefits than TFESI. The base-case analysis yielded total costs of £6,919 (95% CI £5,503, £8,046) and £4,706 (95% CI £3,821, £5,516), and total QALYs of 0.616 (95% CI 0.570, 0.671) and 0.559 (95% CI 0.503, 0.620) for microdiscectomy and TFESI respectively. The mean incremental costs and QALYs (microdiscectomy less TFESI) of £2,212 (95% CI £629, £3,677) and 0.057 (95% CI -0.009, 0.124) resulted in an ICER of £38,737 per QALY gained (Table S28). The probability of microdiscectomy being cost-effective is 0.17 at £20,000 per QALY, and 0.37 at a higher threshold of £30,000 per QALY, indicating that it is unlikely that microdiscectomy is cost-effective compared to TFESI (Figure S3).

**Table S28: Cost-effectiveness at 54 weeks, QALYs, costs (£) and ICER, base-case bootstrapped analysis (mean values with 95%CI)**

|                      | Microdiscectomy | TFESI       | Incremental effect | Cost-effectiveness threshold £20,000 per QALY | £30,000 per QALY |
|----------------------|-----------------|-------------|--------------------|-----------------------------------------------|-----------------|
| Costs (£)            | 6,919 (5,503, 8,046) | 4,706 (3,821, 5,516) | 2,212 (629, 3,677) |                                               |                 |
| QALYs                | 0.616 (0.570, 0.671) | 0.559 (0.503, 0.620) | 0.057 (-0.009, 0.124) |                                               |                 |
| ICER (£/QALY)        | 38,737          |             |                    |                                               |                 |
| Probability          | 0.17            | 0.37        |                    |                                               |                 |
Vertical dotted lines represent the NICE threshold range of £20,000 to £30,000 per QALY.

**Scenario analyses**

None of the scenarios which utilised imputed datasets to address the missing data (that is, all scenarios except the complete case analysis), generated an ICER below the £20,000 per QALY
gained threshold (Table ). In the complete-case analysis (SA2) an ICER of £16,512 per QALY gained was estimated, but owing to the small sample of participants in this analysis (N=35) these results should be interpreted with caution.

When approximating to a societal perspective (SA1), mean total costs increased to £8,353 for microdiscectomy and £6,856 for TFESI, but the difference in mean incremental costs reduced to £1,497. Since there was no difference in incremental QALYs between this scenario and the base-case, including productivity losses had the effect of lowering the ICER to £26,290 per QALY gained. Applying alternative costing approaches for productivity losses, to help address uncertainty in the observed data, (SA10, SA11, SA12) effectively reduced the cost-effectiveness of microdiscectomy by increasing the ICER to £27,981, £32,807 and £36,621 per QALY gained, respectively.

Applying the alternative EQ-5D-5L tariff had minimal effect, but utilising the EQ-VAS scores increased the ICER to £48,113 per QALY gained (SA3, SA4); yet the applicability of the EQ-VAS result is debateable given it is not generally used to inform decision-making.

Taking an alternative approach to costing resource use assuming respondents completed the questionnaire ‘since last completed’, rather than over ‘the last 3 months’ (SA5) reduced the ICER to £35,717 per QALY gained, whilst considering only sciatica-related costs (SA6) had a larger effect, reducing the ICER to £28,251 per QALY gained. The effect of combining sciatica-only costs in a wider perspective (SA9) resulted in a lower ICER of £22,923 per QALY gained. Varying the dose of ‘when needed’ medications to 25% and 75% of the time (SA7, SA8) resulted in ICERS of £41,422 and £36,163 per QALY gained, respectively.
### Table S29: Scenario Analysis, including deterministic results

| Scenario                                                                 | Total cost (£) | Total QALYs | Incremental ICER (£ per QALY gained) |
|--------------------------------------------------------------------------|----------------|-------------|---------------------------------------|
|                                                                          | Microdiscectomy | TFESI       | Microdiscectomy | TFESI | Costs (£) | QALYs gained |
| Basecase<sup>a</sup>                                                     | 6,919          | 4,706       | 0.616          | 0.559 | 2,212     | 0.057        | 38,737       |
| Base-case, deterministic                                                 | 6,941          | 4,701       | 0.617          | 0.560 | 2,240     | 0.057        | 39,344       |
| SA1 Approximating to a societal perspective                             | 8,353          | 6,856       | 0.611          | 0.554 | 1,497     | 0.057        | 26,290       |
| SA2 Complete cases only                                                 | 5,816          | 3,948       | 0.730          | 0.617 | 1,868     | 0.113        | 15,249       |
| SA3 QALYs from 5L valuation set                                         | 6,913          | 4,689       | 0.709          | 0.653 | 2,224     | 0.056        | 39,392       |
| SA4 QALYs inferred from EQ-VAS                                          | 6,925          | 4,702       | 0.690          | 0.644 | 2,222     | 0.046        | 48,113       |
| SA5 Alternative RUQ ‘since last completed’ approach                     | 6,901          | 4,669       | 0.615          | 0.553 | 2,232     | 0.062        | 35,717       |
| SA6 Sciatica-related costs only                                         | 5,920          | 4,299       | 0.616          | 0.558 | 1,620     | 0.057        | 28,251       |
| SA7 ‘When needed’ medications at 25% of BNF recommended dose           | 6,886          | 4,693       | 0.610          | 0.557 | 2,193     | 0.053        | 41,422       |
| SA8 ‘When needed’ medications at 75% of BNF recommended dose           | 6,935          | 4,690       | 0.621          | 0.559 | 2,245     | 0.062        | 36,163       |
| SA9 Approximating to a societal perspective, sciatica costs only        | 7,115          | 5,824       | 0.608          | 0.551 | 1,291     | 0.056        | 22,923       |
| SA10 Approximating to a societal perspective, missing cost of lost days at work based on median salary by age and gender (participants) and postcode salary (carer) | 8,566          | 6,967       | 0.613          | 0.555 | 1,600     | 0.057        | 36,621       |
| SA11 Approximating to a societal perspective, missing RUQ, productivity losses replaced with available clinician recorded employment status and median salary by age and gender | 8,147          | 6,363       | 0.613          | 0.559 | 1,784     | 0.054        | 32,807       |
| SA12 Approximating to a societal perspective, all productivity losses based on reported days lost, costed using median salary by age and gender (participants) and postcode salary (carer) | 10,194         | 8,239       | 0.608          | 0.555 | 1,956     | 0.053        | 36,621       |

<sup>a</sup> Base-case analysis, (non-parametric bootstrapped) approach
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### Supplementary Appendix 6: Safety data

**Table S30: Listing of serious adverse events associated with surgical microdiscectomy**

| System Organ Class (SOC) / Preferred Term (PT) | Onset Date     | Serious Criteria                                                                 | Severity | Expected | Related PI / CI | Action                                                                 | Outcome         |
|-----------------------------------------------|----------------|----------------------------------------------------------------------------------|----------|----------|-----------------|------------------------------------------------------------------------|-----------------|
| Injury, poisoning and procedural complications / Surgical procedure repeated | 25/11/2015     | Required Hospitalisation                                                         | Severe   | Expected | Almost certainly / Almost certainly | Hospital admission, Other action: Redo disc surgery                  | Resolved        |
| Nervous system disorders / Peroneal nerve palsy | 11/02/2017     | Prolonged existing hospitalisation, Persistent or significant disability / incapacity, weakness of foot, further surgical intervention. | Severe   | Expected | Almost certainly / Almost certainly | Treated with concomitant medication, re-explored surgically 12/02/2017 | Ongoing at final follow up |
| Infections and infestations / Postoperative wound infection | 19/09/2017     | Required Hospitalisation                                                         | Severe   | Expected | Almost certainly/ Probably          | Treated with concomitant medication                                 | Resolved        |
| Injury, poisoning and procedural               | 05/12/2016     | Required Hospitalisation                                                         | Moderate | Expected | Almost certainly/                | Treated with concomitant medication, MRI,                             | Resolved        |
| System Organ Class (SOC) / Preferred Term (PT) | Onset Date | Serious Criteria | Severity | Expected | Related PI / CI | Action | Outcome |
|---------------------------------------------|------------|-----------------|----------|----------|----------------|--------|---------|
| complications / Pseudomeningocele           |            |                 |          | Almost certainly | outpatient appointments |        |         |
Supplementary Appendix 7: Details of imputation and sensitivity analyses of primary outcome and secondary outcomes

The multiple imputation sensitivity analysis included treatment group, centre, participant ID, available measurements of ODQ, and number of weeks from randomisation. The fully conditional specification (FCS) model was used. 50 complete data sets were created and combined to generate the imputed model estimate. A post-hoc sensitivity analysis was conducted using multiple imputation (as above) but only using baseline ODQ to impute a week 18 score. The assumption of MAR was explored by an additional post-hoc sensitivity analysis fitting two pattern mixture models, one imputing missing values based only on observations in the TFESI group, and one based only on the surgical microdiscectomy group. Imputed estimates are shown in Table S31. None of the imputed analyses changed the interpretation of the results.

| Analysis                                      | Treatment effect estimate | 95% CI     |
|-----------------------------------------------|---------------------------|------------|
| Initial imputation analysis                   | -3.08                     | -10.16, 3.99|
| Sensitivity – baseline only                   | -3.26                     | -9.91, 3.39 |
| Pattern mixture model using only TFESI group for imputation | -3.17                     | -10.86, 4.52 |
| Pattern mixture model using only surgical microdiscectomy group for imputation | -3.54                     | -10.51, 3.43 |

The primary analysis excluded primary outcome questionnaires received more than 6 weeks from the planned timepoint of 18 weeks. An additional post-hoc sensitivity analysis was carried out including all primary outcome questionnaire received, regardless of time, and is
presented in Table S32. This analysis slightly increased the treatment effect estimate, but did not change the interpretation of the results.

Table S32: Other post-hoc sensitivity analysis for primary outcome

| Analysis                                      | Treatment effect estimate | 95% CI       |
|----------------------------------------------|---------------------------|--------------|
| PO analysis including questionnaires out of window | -5.59                     | -12.08, 0.90 |

Table S33 shows results from sensitivity analyses of the longitudinal analyses, using joint modelling of outcome and dropout, and using an alternative covariance structure (spatial power). Estimates were similar to the main longitudinal analyses.

Table S33: Estimates from longitudinal model including post-hoc sensitivity analyses

| Outcome    | Original model (Treatment effect estimate (95% CI)) | Joint modelling (Treatment effect estimate (95% CI)) | Spatial power covariance structure (Treatment effect estimate (95% CI)) |
|------------|-----------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------|
| ODQ        | -4.67 (-10.61, 1.28)                                | -4.62 (-9.84, 1.27)                                  | -4.59 (-10.40, 1.23)                                                 |
| VAS Leg pain | -7.04 (-15.81, 1.73)                                | -7.06 (-15.82, 0.86)                                 | -6.91 (-15.66, 1.84)                                                 |
| VAS Back pain | -3.01 (-11.29, 5.26)                               | -2.87 (-10.58, 3.16)                                 | -3.25 (-11.35, 4.84)                                                 |
| MRM scores | -1.82 (-3.67, 0.03)                                 | -1.72 (-3.44, 0.10)                                 | -1.72 (-3.53, 0.10)                                                 |
| COMI       | -0.77 (-1.58, 0.03)                                 | -0.78 (-1.54, -0.02)                                | -0.78 (-1.56, -0.002)                                                |