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

**Eudract No: 2014-002751-25**

**ISRCTN: 04820368**

**Final Analysis Report V2.0**

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**Change Control**

| Updated shell version no. | Shell section changed | Description of change | Date changed | Initials |
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| 2.0 | 6.8.2.2<br>6.8.3.2<br>6.8.4.2<br>6.8.6.2<br>6.8.7.2 | Addition of the post-hoc joint modelling outcomes for all longitudinal outcomes. For ODQ longitudinal outcome addition of baseline ODQ scores by dropout status. | 25/11/2019 | AB |

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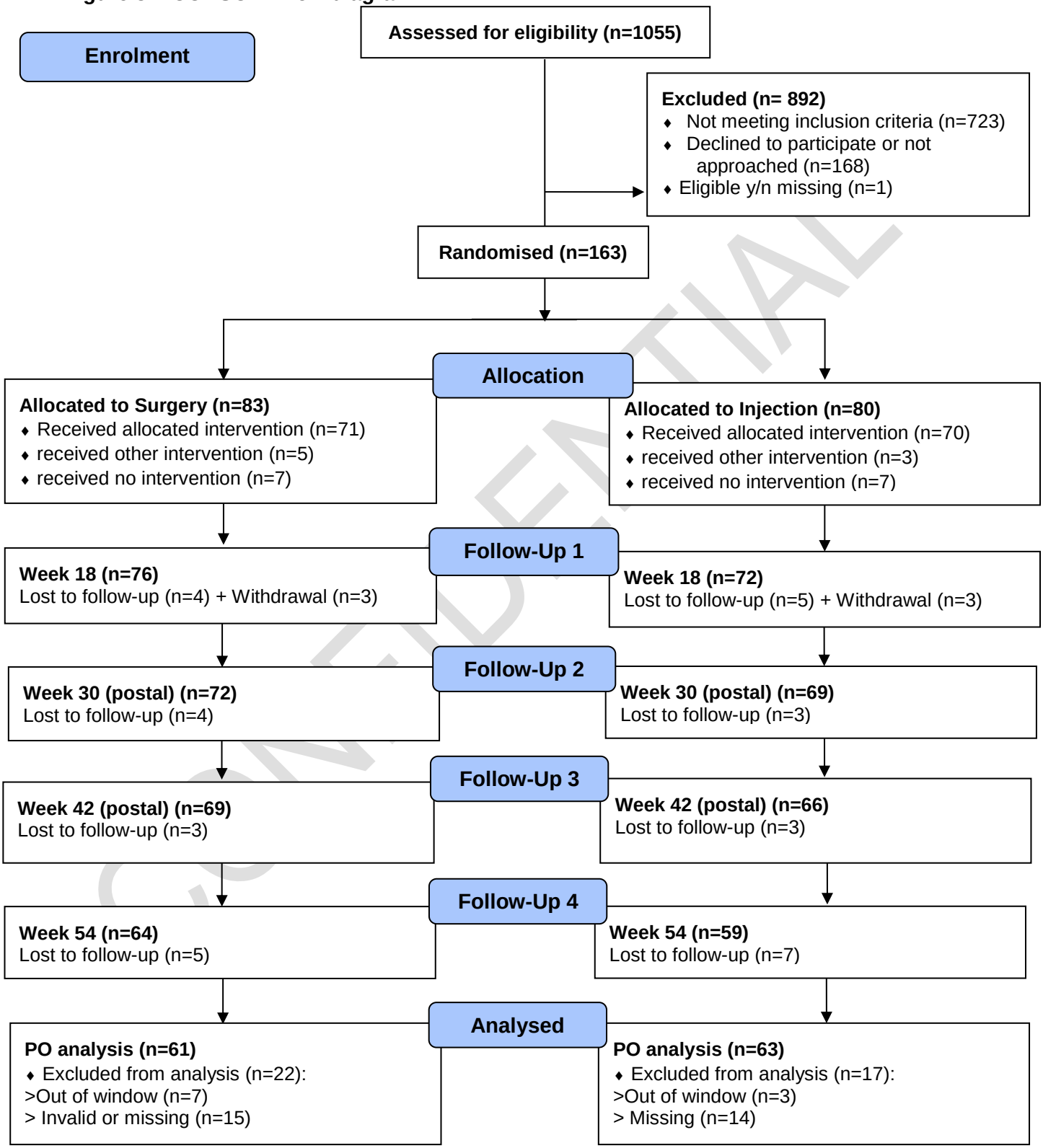
## 3. CONSORT diagram

### 3.1 Flow Diagram

**Figure 3-1 CONSORT flow diagram**

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## 4. Randomisation

### 4.1 Randomisation checks

There were no out of sequence or missing randomisation numbers.

## 5. Recruitment and screening

### 5.1 Screening summary

**Table 5-1 Summary of screening logs**

| Centre Code | Hospital | Date site opened | Number of patients screened<br>*[N]*<br>N | Eligible A<br>*[a]*<br>n (%) | Ineligible B<br>*[b]*<br>n (%) | Consent provided C<br>*[c]*<br>n (%) | Consent not provided D<br>*[d]*<br>n (%) | Consent provided but patient not randomised E<br>*[e]*<br>n (%) | Randomised F<br>*[f]*<br>n (%) |
|---|---|---|---|---|---|---|---|---|---|
| 0006 | James Cook Hospital | 01/04/2016 | 28 | 27 (96.43%) | 1 (3.57%) | 14 (51.85%) | 13 (48.15%) | 0 | 14 (100.0%) |
| 0007 | Addenbrookes Hospital | 14/07/2016 | 23 | 23 (100.0%) | 0 (0.000%) | 11 (47.83%) | 12 (52.17%) | 0 | 11 (100.0%) |
| 0093 | Royal Hallamshire Hospital | 15/08/2016 | 116 | 16 (13.79%) | 100 (86.21%) | 6 (37.50%) | 10 (62.50%) | 0 | 6 (100.0%) |
| 0137 | Barts Health NHS Trust | 08/08/2016 | 33 | 0 (0.000%) | 33 (100.0%) | 0 | 0 | 0 | 0 |
| 0160 | Royal Preston | 01/12/2015 | 287 | 8 (2.787%) | 279 (97.21%) | 1 (12.50%) | 7 (87.50%) | 0 | 1 (100.0%) |
| 0182 | Royal Stoke University Hospital | 29/07/2016 | 5 | 5 (100.0%) | 0 (0.000%) | 1 (20.00%) | 4 (80.00%) | 0 | 1 (100.0%) |
| 0213 | Nottingham University hospital | 27/09/2017 | 8 | 8 (100.0%) | 0 (0.000%) | 8 (100.0%) | 0 (0.000%) | 0 | 8 (100.0%) |

| Centre Code | Hospital | Date site opened | Number of patients screened | Eligible A | Ineligible B | Consent provided C | Consent not provided D | Consent provided but patient not randomised E | Randomised F |
|---|---|---|---|---|---|---|---|---|---|
| | | | *[N]* N | *[a]* n (%) | *[b]* n (%) | *[c]* n (%) | *[d]* n (%) | *[e]* n (%) | *[f]* n (%) |
| 0400 | Salford Royal | 13/04/2015 | 52 | 20 (38.46%) | 32 (61.54%) | 9 (45.00%) | 11 (55.00%) | 0 | 9 (100.0%) |
| 0428 | The Royal Orthopaedic Hospital, Birmingham | 07/10/2015 | 138 | 32 (23.19%) | 106 (76.81%) | 6 (18.75%) | 26 (81.25%) | 0 | 6 (100.0%) |
| 0492 | Seacroft Leeds | 02/03/2016 | 138 | 55 (39.86%) | 83 (60.14%) | 14 (25.45%) | 41 (74.55%) | 0 | 14 (100.0%) |
| 0578 | Walton Centre | 04/03/2015 | 186 | 103 (55.38%) | 82 * (44.09%) | 80 (77.67%) | 23 (22.33%) | 0 | 80 (100.0%) |
| 3253 | Solent MSK Services | 01/04/2016 | 41 | 34 (82.93%) | 7 (17.07%) | 13 (38.24%) | 21 (61.76%) | 0 | 13 (100.0%) |
| | | **Total** | **1055** | **331 (31.37%)** | **723 * (68.53%)** | **163 (49.24%)** | **168 (50.76%)** | **0** | **163 (100.0%)** |

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***Note:** Eligible y/n now missing for one patient at site 0578*

**Calculating %s**

| Item | | Equation |
|---|---|---|
| A | Percent eligible | a/N |
| B | Percent ineligible | b/N |
| C | Percent consent provided | c/a |
| D | Percent consent not provided | d/a |
| E | Percent consent provided but not randomised | e/c |
| F | Percent randomised | f/c |

## 5.2 Ineligible patients

**Table 5-2 Reasons for ineligibility 1**

| Patient count N (% of total ineligible per site) | Total number of ineligible patients | Reasons for ineligibility [a,b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R01 | R02 | R03 | R04 | R05 | R06 | R07 | R08 |
| Overall [c] | 723 | 174 (24.07%) | 9 (1.24%) | 107 (14.80%) | 57 (7.88%) | 0 (0.00%) | 61 (8.44%) | 25 (3.46%) | 62 (8.58%) |
| James Cook Hospital (0006) | 1 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Royal Hallamshire Hospital (0093) | 100 | 0 (0.00%) | 2 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 35 (35.00%) | 0 (0.00%) | 8 (8.00%) |
| Barts Health NHS Trust (0137) | 33 | 0 (0.00%) | 1 (3.03%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (3.03%) | 0 (0.00%) | 4 (12.12%) |
| Royal Preston (0160) | 279 | 111 (39.78%) | 0 (0.00%) | 56 (20.07%) | 17 (6.09%) | 0 (0.00%) | 7 (2.51%) | 1 (0.36%) | 28 (10.04%) |
| Salford Royal (0400) | 32 | 4 (12.50%) | 1 (3.13%) | 10 (31.25%) | 8 (25.00%) | 0 (0.00%) | 0 (0.00%) | 2 (6.25%) | 3 (9.38%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| The Royal Orthopaedic Hospital, Birmingham (0428) | 106 | 38 (35.85%) | 0 (0.00%) | 28 (26.42%) | 14 (13.21%) | 0 (0.00%) | 5 (4.72%) | 12 (11.32%) | 0 (0.00%) |
| Seacroft Leeds (0492) | 83 | 5 (6.02%) | 0 (0.00%) | 1 (1.20%) | 3 (3.61%) | 0 (0.00%) | 12 (14.46%) | 6 (7.23%) | 14 (16.87%) |
| Walton Centre (0578) | 82 | 16 (19.51%) | 5 (6.10%) | 12 (14.63%) | 15 (18.29%) | 0 (0.00%) | 1 (1.22%) | 0 (0.00%) | 5 (6.10%) |
| Solent MSK Services (3253) | 7 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 4 (57.14%) | 0 (0.00%) |

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[a] Ineligible patients may fail on 1 or more reasons for ineligibility.
[b] Reasons for ineligibility 1-8:

R01. Patient hasn't had sciatica secondary PID proven on MRI scan (1A)
R02. Patient symptoms have occurred for less than six weeks (1B)
R03. Patient symptoms have occurred for more than 6 months (1C)
R04. Patient doesn't have leg pain which is non responsive to conservative non-invasive management (1D)
R05. Patient is under 16 years old (1E)
R06. Patient is over 65 years old (1F)
R07. Patient has attempted at least one form of conservative (non-operative) treatment but this has not provided adequate relief of patient's pain (1G) **OR** Patient has not attempted any form of conservative non-operative treatment (1K)
R08. Patient has serious neurological deficit (1H)

[c] Only sites that have screened at least one ineligible patient are included in table.

**Table 5-3 Reason for ineligibility 2**

| Patient count N (% of total ineligible per site) | Total number of ineligible patients | Reasons for ineligibility [a,b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R09 | R10 | R11 | R12 | R13 | R14 | R15 | R16 |
| Overall [c] | 723 | 97 (13.42%) | 19 (2.63%) | 5 (0.69%) | 35 (4.84%) | 26 (3.60%) | 73 (10.10%) | 50 (6.92%) | 3 (0.41%) |
| James Cook Hospital (0006) | 1 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (100.00%) | 0 (0.00%) | 0 (0.00%) |
| Royal Hallamshire Hospital (0093) | 100 | 44 (44.00%) | 0 (0.00%) | 1 (1.00%) | 3 (3.00%) | 0 (0.00%) | 36 (36.00%) | 25 (25.00%) | 0 (0.00%) |
| Barts Health NHS Trust (0137) | 33 | 8 (24.24%) | 0 (0.00%) | 0 (0.00%) | 5 (15.15%) | 5 (15.15%) | 7 (21.21%) | 6 (18.18%) | 0 (0.00%) |
| Royal Preston (0160) | 279 | 10 (3.58%) | 4 (1.43%) | 1 (0.36%) | 19 (6.81%) | 20 (7.17%) | 1 (0.36%) | 5 (1.79%) | 0 (0.00%) |
| Salford Royal (0400) | 32 | 4 (12.50%) | 0 (0.00%) | 0 (0.00%) | 1 (3.13%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| The Royal Orthopaedic Hospital, Birmingham (0428) | 106 | 1 (0.94%) | 7 (6.60%) | 2 (1.89%) | 4 (3.77%) | 0 (0.00%) | 2 (1.89%) | 4 (3.77%) | 0 (0.00%) |
| Seacroft Leeds (0492) | 83 | 23 (27.71%) | 8 (9.64%) | 0 (0.00%) | 1 (1.20%) | 0 (0.00%) | 10 (12.05%) | 8 (9.64%) | 0 (0.00%) |

| Patient count N (% of total ineligible per site) | Total number of ineligible patients | Reasons for ineligibility [a,b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R09 | R10 | R11 | R12 | R13 | R14 | R15 | R16 |
| Walton Centre (0578) | 82 | 7 (8.54%) | 0 (0.00%) | 1 (1.22%) | 2 (2.44%) | 1 (1.22%) | 13 (15.85%) | 2 (2.44%) | 3 (3.66%) |
| Solent MSK Services (3253) | 7 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (42.86%) | 0 (0.00%) | 0 (0.00%) |

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[a] Ineligible patients may fail on 1 or more reasons for ineligibility.
[b] Reasons for ineligibility 9-16:

R09: Patient has had previous spinal surgery at the same intervertebral disc (level) (1I)
R10. Patient has had sciatica for longer than 6 months (1J)
R11: Patient is known to be pregnant (1L)
R12: Patient has a contraindication to surgery (1M)
R13: Patient has a contraindication to injection (1N)
R14: Patients symptoms have occurred for more than 12 months (1O)
R15: Patient has had sciatica for longer than 12 months (1P)
R16: No reason given

[c] Only sites that have screened at least one ineligible patient are included in table.

### 5.3 Patients not being consented

Patients can not be consented because they are either not approached for consent or the patient declined to provide consent, below are the summaries of the reasons why in each of these cases separately.

**Table 5-4 Reason eligible patient were not approached for consent**

| Patient count N (% of total patient not being approached per site) | Total | Reasons consent not sought [a,b] | | | |
|---|---|---|---|---|---|
| | | CNS01 | CNS02 | CNS03 | CNS04 [d] |
| Overall [c] | 24 | 0 (0.00%) | 1 (4.17%) | 2 (8.33%) | 21 (87.50%) |
| Addenbrookes Hospital (0007) | 2 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (100.00%) |
| Royal Hallamshire Hospital (0093) | 1 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (100.00%) |
| Royal Preston (0160) | 3 | 0 (0.00%) | 1 (33.33%) | 0 (0.00%) | 2 (66.67%) |
| Royal Stoke University Hospital (0182) | 1 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (100.00%) |
| The Royal Orthopaedic Hospital, Birmingham (0428) | 13 | 0 (0.00%) | 0 (0.00%) | 1 (7.69%) | 12 (92.31%) |
| Seacroft Leeds (0492) | 2 | 0 (0.00%) | 0 (0.00%) | 1 (50.00%) | 1 (50.00%) |
| Solent MSK Services (3253) | 2 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (100.00%) |

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[a] Consent may not be sought for more than one reason.
[b] Reasons consent not sought:
CNS01. Missed by research nurse/doctor
CNS02. Not approached because of patients lack of understanding
CNS03. Not approached for consultant preference
CNS04. Not approached for other reason
[c] Only sites which have screened at least one eligible patient was not approached for consent included in the table.
[d] See appendix for other reasons

**Table 5-5 Reasons for eligible patient declining to participate**

| Patient count N (% of total consent not provided by site) | Total consent not provided | Reasons consent not provided [a,b] | | | | |
|---|---|---|---|---|---|---|
| | | CNP01 | CNP02 | CNP03 | CNP04 | CNP05 |
| Overall [c] | 143 | 3 (2.10%) | 33 (23.08%) | 60 (41.96%) | 22 (15.38%) | 33 (23.08%) |
| James Cook Hospital (0006) | 13 | 0 (0.00%) | 0 (0.00%) | 13 (100.00%) | 0 (0.00%) | 0 (0.00%) |
| Addenbrookes Hospital (0007) | 10 | 2 (20.00%) | 2 (20.00%) | 1 (10.00%) | 5 (50.00%) | 0 (0.00%) |
| Royal Hallamshire Hospital (0093) | 9 | 0 (0.00%) | 1 (11.11%) | 0 (0.00%) | 5 (55.56%) | 3 (33.33%) |
| Royal Preston (0160) | 4 | 0 (0.00%) | 2 (50.00%) | 1 (25.00%) | 1 (25.00%) | 0 (0.00%) |
| Royal Stoke University Hospital (0182) | 3 | 0 (0.00%) | 1 (33.33%) | 3 (100.00% | 1 (33.33%) | 1 (33.33%) |
| Salford Royal (0400) | 11 | 0 (0.00%) | 2 (18.18%) | 3 (27.27%) | 4 (36.36%) | 3 (27.27%) |
| The Royal Orthopaedic Hospital, Birmingham (0428) | 13 | 0 (0.00%) | 4 (30.77%) | 1 (7.69%) | 0 (0.00%) | 8 (61.54%) |
| Seacroft Leeds (0492) | 39 | 0 (0.00%) | 19 (48.72%) | 19 (48.72%) | 2 (5.13%) | 2 (5.13%) |
| Walton Centre (0578) | 22 | 0 (0.00%) | 1 (4.55%) | 12 (54.55%) | 2 (9.09%) | 7 (31.82%) |
| Solent MSK Services (3253) | 19 | 1 (5.26%) | 1 (5.26%) | 7 (36.84%) | 2 (10.53%) | 9 (47.37%) |

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[a] Patients may not provide consent for more than one reason.
[b] Reasons consent not provided:

CNP01. No reason provided – 2A
CNP02. Doesn't want to take part in research – 2B
CNP03. Doesn't wish to be randomly assigned to treatment – 2C
CNP04. Doesn't wish to have TFESI – 2D
CNP05. Doesn't wish to have surgical microdiscectomy – 2E

[c] Only sites that have screened at least one eligible patient who declined consent included in the table.

### 5.4 Randomisation Summary

**Table 5-6 Summary of randomisation by site**

| Centre Code | Hospital | Date site opened | Date site closed | Surgical Microdiscectomy (Surgery) | | | TFESI (Injection) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | First randomised | Last randomised | Total | First randomised | Last randomised | Total |
| 0006 | James Cook Hospital | 01/04/2016 | 31/12/2017 | 12/05/2016 | 02/10/2017 | 7 | 12/05/2016 | 14/12/2017 | 7 |
| 0007 | Addenbrookes Hospital | 14/07/2016 | 31/12/2017 | 09/09/2016 | 19/10/2017 | 6 | 15/11/2016 | 30/11/2017 | 5 |
| 0093 | Royal Hallamshire Hospital | 15/08/2016 | 31/12/2017 | 03/05/2017 | 13/12/2017 | 3 | 21/09/2016 | 12/07/2017 | 3 |
| 0160 | Royal Preston | 01/12/2015 | 31/12/2017 | 17/02/2017 | 17/02/2017 | 1 | N/A | N/A | 0 |
| 0182 | Royal Stoke University Hospital | 29/07/2016 | 31/12/2017 | 21/11/2017 | 21/11/2017 | 1 | N/A | N/A | 0 |
| 0213 | Nottingham University hospital | 27/09/2017 | 31/12/2017 | 20/10/2017 | 21/12/2017 | 4 | 20/10/2017 | 21/12/2017 | 4 |
| 0400 | Salford Royal | 13/04/2015 | 31/12/2017 | 03/08/2015 | 04/08/2016 | 4 | 14/04/2015 | 02/02/2017 | 5 |
| 0428 | The Royal Orthopaedic Hospital, Birmingham | 07/10/2015 | 31/12/2017 | 26/10/2015 | 05/06/2017 | 3 | 13/01/2016 | 14/02/2017 | 3 |
| 0492 | Seacroft Leeds | 02/03/2016 | 31/12/2017 | 13/09/2016 | 08/08/2017 | 7 | 29/09/2016 | 08/06/2017 | 7 |
| 0578 | Walton Centre | 04/03/2015 | 31/12/2017 | 06/03/2015 | 25/09/2017 | 40 | 06/03/2015 | 04/08/2017 | 40 |
| 3253 | Solent MSK Services | 01/04/2016 | 31/12/2017 | 13/07/2016 | 25/09/2017 | 7 | 20/06/2016 | 12/04/2017 | 6 |
| | | | **Overall** | **06/03/2015** | **21/12/2017** | **83** | **06/03/2015** | **21/12/2017** | **80** |

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## 6. Tables

### 6.1 Baseline characteristics

#### 6.1.1 Demographic details

**Table 6-1 All demographic details split by allocation**

| Demographic | Summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Gender, n(%) | N | 83 | 80 | 163 |
| | Female | 46 (55.4%) | 40 (50.0%) | 86 (52.8%) |
| | Male | 37 (44.6%) | 40 (50.0%) | 77 (47.2%) |
| Age (continuous) Summary | N | 83 | 80 | 163 |
| | Mean (S.D.) | 43.5 (9.9) | 41.2 (8.6) | 42.4 (9.3) |
| | Median (IQR) | 42.8 (34.9-50.5) | 41.4 (35.2-47.0) | 42.2 (35.2-48.9) |
| | Range | 23.2 - 65.6 | 23.3 - 59.8 | 23.2 - 65.6 |
| | Data unobtainable | 0 | 0 | 0 |
| Age (EudraCT), n(%) | N | 83 | 80 | 163 |
| | 18-65 years | 82 (98.8%) | 80 (100.0%) | 162 (99.4%) |
| | 65-84 years | 1 (1.2%) | 0 (0.0%) | 1 (0.6%) |
| Of reproductive potential, n(%) | N | 46 | 40 | 86 |
| | No | 11 (23.9%) | 5 (12.5%) | 16 (18.6%) |
| | Yes | 35 (76.1%) | 35 (87.5%) | 70 (81.4%) |
| Taking Anticoagulant Medication, n(%) | N | 83 | 80 | 163 |
| | No | 82 (98.8%) | 79 (98.8%) | 161 (98.8%) |
| | Yes | 1 (1.2%) | 1 (1.3%) | 2 (1.2%) |
| Previous surgery at disc level, n(%) | N | 83 | 80 | 163 |
| | No | 82 (98.8%) | 80 (100.0%) | 162 (99.4%) |
| | Yes | 1 (1.2%) | 0 (0.0%) | 1 (0.6%) |
| No. of weeks of symptoms Summary | N | 83 | 80 | 163 |
| | Mean (S.D.) | 21.5 (10.7) | 21.1 (11.2) | 21.3 (10.9) |
| | Median (IQR) | 17.0 (14.0-28.0) | 18.0 (13.0-27.0) | 18.0 (14.0-28.0) |

| | | | | |
|---|---|---|---|---|
| | Range | 7.0 - 51.0 | 8.0 - 64.0 | 7.0 - 64.0 |
| | Data unobtainable | 0 | 0 | 0 |
| Has patient taken medication for pain and symptoms, n(%) | N | 83 | 80 | 163 |
| | Yes | 83 (100.0%) | 80 (100.0%) | 163 (100.0%) |
| Has patient modified activity, n(%) | N | 83 | 80 | 163 |
| | No | 0 (0.0%) | 1 (1.3%) | 1 (0.6%) |
| | Yes | 83 (100.0%) | 79 (98.8%) | 162 (99.4%) |
| Has patient attended physiotherapy, n(%) | N | 83 | 80 | 163 |
| | No | 15 (18.1%) | 16 (20.0%) | 31 (19.0%) |
| | Yes | 68 (81.9%) | 64 (80.0%) | 132 (81.0%) |
| Has patient had other conservative (non operative) treatment for pain and symptoms, n(%) | N | 83 | 80 | 163 |
| | No | 49 (59.0%) | 43 (53.8%) | 92 (56.4%) |
| | Yes | 34 (41.0%) | 37 (46.3%) | 71 (43.6%) |
| Estimated volume of canal occupied by disc prolapse, n(%) | N | 83 | 80 | 163 |
| | Less than 25% | 43 (51.8%) | 44 (55.0%) | 87 (53.4%) |
| | Between 25%-50% | 36 (43.4%) | 34 (42.5%) | 70 (42.9%) |
| | Greater than 50% | 4 (4.8%) | 2 (2.5%) | 6 (3.7%) |
| Weight (Kg) Summary | N | 75 | 71 | 146 |
| | Mean (S.D.) | 83.7 (16.8) | 81.4 (20.7) | 82.6 (18.8) |
| | Median (IQR) | 82.0 (72.0-95.1) | 77.1 (67.0-94.0) | 79.3 (69.8-94.0) |
| | Range | 54.0 - 134.0 | 51.7 - 154.0 | 51.7 - 154.0 |
| | Data unobtainable | 8 | 9 | 17 |
| Height (cm) Summary | N | 76 | 71 | 147 |
| | Mean (S.D.) | 171.7 (10.7) | 172.6 (9.5) | 172.2 (10.1) |
| | Median (IQR) | 170.1 (164.0-180.7) | 173.0 (167.0-180.0) | 171.5 (165.0-180.0) |
| | Range | 147.0 - 197.0 | 150.0 - 192.0 | 147.0 - 197.0 |
| | Data unobtainable | 7 | 9 | 16 |
| BMI (Kg / $m^2$) | N | 74 | 68 | 142 |

| | | | | |
|---|---|---|---|---|
| | Mean (S.D.) | 28.2 (5.3) | 27.2 (6.4) | 27.7 (5.9) |
| | Median (IQR) | 26.9 (24.5-31.3) | 25.6 (22.9-29.4) | 26.4 (24.1-30.7) |
| | Range | 18.9 - 44.3 | 17.1 - 47.1 | 17.1 - 47.1 |
| | Data unobtainable | 9 | 12 | 21 |
| Posture, n(%) | N | 83 | 80 | 163 |
| | Abnormal | 38 (45.8%) | 41 (51.3%) | 79 (48.5%) |
| | Normal | 43 (51.8%) | 37 (46.3%) | 80 (49.1%) |
| | Not Done | 2 (2.4%) | 2 (2.5%) | 4 (2.5%) |
| Range of movement, n(%) | N | 83 | 80 | 163 |
| | Abnormal | 52 (62.7%) | 50 (62.5%) | 102 (62.6%) |
| | Normal | 27 (32.5%) | 27 (33.8%) | 54 (33.1%) |
| | Not Done | 4 (4.8%) | 3 (3.8%) | 7 (4.3%) |
| Muscle strength, n(%) | N | 83 | 80 | 163 |
| | Abnormal | 12 (14.5%) | 18 (22.5%) | 30 (18.4%) |
| | Normal | 67 (80.7%) | 59 (73.8%) | 126 (77.3%) |
| | Not Done | 4 (4.8%) | 3 (3.8%) | 7 (4.3%) |
| Left ankle jerks present, n(%) | N | 83 | 80 | 163 |
| | No | 13 (15.7%) | 11 (13.8%) | 24 (14.7%) |
| | Yes | 68 (81.9%) | 66 (82.5%) | 134 (82.2%) |
| | Data unobtainable | 2 (2.4%) | 3 (3.8%) | 5 (3.1%) |
| Right ankle jerks present, n(%) | N | 83 | 80 | 163 |
| | No | 13 (15.7%) | 13 (16.3%) | 26 (16.0%) |
| | Yes | 68 (81.9%) | 66 (82.5%) | 134 (82.2%) |
| | Data unobtainable | 2 (2.4%) | 1 (1.3%) | 3 (1.8%) |
| Left knee jerks present, n(%) | N | 83 | 80 | 163 |
| | No | 2 (2.4%) | 4 (5.0%) | 6 (3.7%) |
| | Yes | 79 (95.2%) | 73 (91.3%) | 152 (93.3%) |
| | Data unobtainable | 2 (2.4%) | 3 (3.8%) | 5 (3.1%) |
| Right knee jerks present, n(%) | N | 83 | 80 | 163 |

| | | | | |
|---|---|---|---|---|
| | No | 3 (3.6%) | 5 (6.3%) | 8 (4.9%) |
| | Yes | 78 (94.0%) | 74 (92.5%) | 152 (93.3%) |
| | Data unobtainable | 2 (2.4%) | 1 (1.3%) | 3 (1.8%) |
| SLR reduction present, n(%) | N | 83 | 80 | 163 |
| | No | 6 (7.2%) | 4 (5.0%) | 10 (6.1%) |
| | Yes | 75 (90.4%) | 76 (95.0%) | 151 (92.6%) |
| | Data unobtainable | 2 (2.4%) | 0 (0.0%) | 2 (1.2%) |
| Location of SLR reduction present, n(%) | N | 75 | 76 | 151 |
| | Bilateral | 7 (9.3%) | 9 (11.8%) | 16 (10.6%) |
| | Unilateral (Left) | 37 (49.3%) | 39 (51.3%) | 76 (50.3%) |
| | Unilateral (Right) | 31 (41.3%) | 28 (36.8%) | 59 (39.1%) |
| Any other abnormalities present, n(%) | N | 83 | 80 | 163 |
| | No | 63 (75.9%) | 59 (73.8%) | 122 (74.8%) |
| | Yes | 19 (22.9%) | 21 (26.3%) | 40 (24.5%) |
| | Data unobtainable | 1 (1.2%) | 0 (0.0%) | 1 (0.6%) |
| Is patient currently employed, n(%) | N | 83 | 80 | 163 |
| | No | 21 (25.3%) | 13 (16.3%) | 34 (20.9%) |
| | Yes | 62 (74.7%) | 66 (82.5%) | 128 (78.5%) |
| | Data unobtainable | 0 (0.0%) | 1 (1.3%) | 1 (0.6%) |
| Is patient currently unable to work due to sciatica, n(%) | N | 62 | 66 | 128 |
| | No | 41 (66.1%) | 34 (51.5%) | 75 (58.6%) |
| | Yes | 21 (33.9%) | 32 (48.5%) | 53 (41.4%) |
| Is the patient is currently taking analgesics/ steroids/ anticoagulant medication, n(%) | N | 83 | 80 | 163 |
| | No | 7 (8.4%) | 7 (8.8%) | 14 (8.6%) |
| | Yes | 76 (91.6%) | 73 (91.3%) | 149 (91.4%) |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\02B-Baseline.SAS*

## 6.2 Study population

### 6.2.1 Data sets analysed

**Table 6-2 Data sets analysed**

| Population | Surgery | Injection | Total |
|---|---|---|---|
| Screened | 1055 (total) | 1055 (total) | 1055 |
| Randomised | 83 | 80 | 163 |
| Intention-to-treat | 83 (100%) | 80 (100%) | 163 (100%) |
| Per-protocol | N/A | N/A | N/A |
| Safety | 105 (64.4%) | 82 (50.3%) | 155 (95.1%) |

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### 6.2.2 Protocol deviations

**Table 6-3 Protocol deviations**

| Protocol deviations: n (%) | Surgery | Injection | Total |
|---|---|---|---|
| N | 83 | 80 | 163 |
| Any protocol deviation | 69 (83.1%) | 74 (92.5%) | 143 (87.7%) |
| At least one major: | 26 (31.3%) | 20 (25.0%) | 46 (28.2%) |
| Duration of symptoms between 6 weeks and 12 months* | 0 (1.4%) | 1 (1.4%) | 1 (0.6%) |
| Severe leg pain non-responsive to conservative, non invasive management | 1 (1.2%) | 0 (0.0%) | 1 (0.6%) |
| Previous spinal surgery at the same intervertebral disc (level) | 1 (1.2%) | 0 (0.0%) | 1 (0.6%) |
| Treatment compliance | 12 (14.5%) | 10 (12.5%) | 22 (13.5%) |
| Treatment timeline compliance | 6 (7.2%) | 1 (1.3%) | 7 (4.3%) |
| Missing primary outcome questionnaire | 14 (16.9%) | 14 (17.5%) | 28 (17.2%) |
| Protocol specified assessment tools not used** | 3 (1.3%) | 1 (1.3%) | 4 (2.5%) |
| At least one minor: | 67 (80.7%) | 71 (88.8%) | 138 (84.7%) |

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***** Exclusion criteria extended from 6 months to 12 months, PD occurred when inclusion criteria was at 12 months.
****** no longer protocol deviation under current version of protocol but still reportable for occurrences earlier in study.

### 6.3 Withdrawals

In total, there were 6 withdrawals of consent for follow up during the study, 3 of these were in the surgery arm and 3 were in the injection arm. There were no complete data withdrawals.

**Table 6-4 Withdrawals from follow up**

| Allocation | Withdrawal date | Last visit date | Decision by | Level / reason(s) |
|---|---|---|---|---|
| TFESI | 29-Jan-18 | 29-Jan-18 | Clinician | Pt unwilling to have injection or surgery |
| Surgical Microdiscectomy | 08-May-18 | 31-Jan-18 | Participant | Withdrawal of consent for ALL further follow-up<br><br>Participant is not happy with the process and will not pick all my phone calls. |
| TFESI | 01-Jun-18 | 08-Nov-17 | Clinician | Site has exhausted all means of communication with the participant, with participant failing to make contact or comply with site requests. |
| Surgical Microdiscectomy | 22-Jun-16 | 21-Jun-16 | Participant | Withdrawal of consent for follow up |
| TFESI | 18-Apr-17 | 18-Apr-17 | Clinician | chest infection and investigation for possible bowel cancer delayed treatment |
| Surgical Microdiscectomy | 24-Jan-17 | 24-Jan-17 | Clinician and Participant | Withdrawal of consent for follow up |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\07A-FU TC.sas*

### 6.4 Serious breaches of GCP

There was one confirmed serious breach of GCP during NERVES. See section 16.3 – Serious Breach reports (report no. 002) for full details of the breach. below is an outline of the events:

During the course of the trial a serious breach occurred at a participating centre. It was identified as a systematic failure to follow the protocol and a breach of data integrity for the following reasons:

- Data not recorded in notes:
    - At the time of initial assessment of the breach it was thought that the case report forms (CRFs) had been used as source. Upon further investigation that was not the case, data had been recorded elsewhere however there was a long delay in writing it up / transferring to the electronic medical notes.
- Missing primary outcome data
- Failure to comply with protocol timeline requirements
- Failure to flag to LCTC issues with treatment, follow-up of patients and site data collection
- Inclusion of 3 ineligible patients

None of the issues identified had any implications for patient safety. LCTC advised the centre of appropriate corrective and preventative actions that needed to be completed to address the issues identified; all have been completed and the MHRA have confirmed they consider the serious breach closed.

## 6.5 Compliance with treatment

For treatment timeline, the protocol specifies that treatment should be received within 6 weeks but no later than 12 week

**Table 6-5 Timing of treatment**

| Treatment timeline compliance | Summary | Allocation | |
|---|---|---|---|
| | | Surgery | Injection |
| **Within 6 weeks or no treatment received** | N | 57 | 75 |
| | % | 68.67 | 93.75 |
| **Between 6 to 12 weeks** | N | 20 | 4 |
| | % | 24.1 | 5 |
| **Greater than 12 weeks** | N | 6 | 1 |
| | % | 7.23 | 1.25 |
| | **Total** | **83** | **80** |

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**Table 6-6 Details for patients not receiving allocated treatment**

| Allocation | Received Allocated | Actually received | Details |
|---|---|---|---|
| Surgical Microdiscectomy | No | TFESI | Other<br>anaesthetist decided wasn't safe for surgery |
| Surgical Microdiscectomy | No | TFESI | Patient preference<br>TFESI |
| Surgical Microdiscectomy | No | TFESI | Other<br>severe sciatic pain down the right leg had resolved. Surgery would be inappropriate. |
| Surgical Microdiscectomy | No | TFESI | Patient preference<br>patient declined following reflection preferred TFESI |
| TFESI | No | Surgical Microdiscectomy | Patient preference |
| TFESI | No | Surgical Microdiscectomy | Patient preference<br>The change to surgical microdiscectomy was patient preference following randomisation. |
| Surgical Microdiscectomy | No | TFESI | Patient preference<br>declined surgery |
| TFESI | No | Surgical Microdiscectomy | Other<br>Surgeon decision |

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**Table 6-7 details of trial interventions received**

| Details | Surgery n=83 | Injection n=80 |
|---|---|---|
| | n (%) | n (%) |
| **Received randomised treatment initially** | | |
| Single randomised treatment | 65 (78.31) | 40 (50) |
| Repeated randomised treatment | 3 (3.61) | 2 (2.5) |
| Randomised treatment then the alternative treatment at least once | 3 (3.61) | 28 (35) |
| **Received alternative treatment initially** | | |
| Single alternative treatment | 3 (3.61) | 3 (3.75) |
| Repeated alternative treatment | 1 (1.2) | 0 |
| Alternative treatment then the randomised treatment | 1 (1.2) | 0 |
| **Late/ no treatment** | | |
| No treatment recorded during trial | 4 (4.82) | 4 (5) |
| Late randomised treatment | 0 | 1 (1.25) |
| Late alternative treatment(s) | 3 | 2 (2.5) |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\07A-FU TC.sas*

Red text denotes patients who crossed arms during the study.

**Table 6-8 Treatment cross-over in relation to primary outcome**

| Cross-overs | Summary | Randomised treatment | |
|---|---|---|---|
| | | Surgery n=83 | Injection n=80 |
| Cross-over after PO | N | 2 | 13 |
| | % | 2.41 | 16.25 |
| Cross-over before PO | N | 2 | 13 |
| | % | 2.41 | 16.25 |
| **Total** | **N** | **4** | **26** |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\07A-FU TC.sas*

## 6.6 Unblinding

N/A as NERVES is an open-label trial.

## 6.7 Safety data

### 6.7.1 Adverse events

**Table 6-9 Adverse events overall**

| Adverse event | | Surgery (n=105) | | Injection (n=82) | | Overall (n=155) | |
|---|---|---|---|---|---|---|---|
| **System organ class (SOC)** | **Preferred term (PT)** | **Events: n** | **Patients: n(%)** | **Events: n** | **Patients: n(%)** | **Events: n** | **Patients: n(%)** |
| | **Total** | **18** | **15 (14.29%)** | **8** | **3 (3.66%)** | **26** | **18 (11.61%)** |
| Nervous system disorders | Hypoaesthesia | 1 | 1 (0.95%) | 5 | 2 (2.44%) | 6 | 3 (1.94%) |
| | Cerebrospinal fluid leakage | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Peroneal nerve palsy | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Radicular pain | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| Injury, poisoning and procedural complications | Dural tear | 4 | 4 (3.81%) | 0 | 0 (0.00%) | 4 | 4 (2.58%) |
| | Pseudomeningocele | 2 | 2 (1.90%) | 0 | 0 (0.00%) | 2 | 2 (1.29%) |
| | Surgical procedure repeated | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Wound complication | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| Infections and infestations | Postoperative wound infection | 2 | 2 (1.90%) | 0 | 0 (0.00%) | 2 | 2 (1.29%) |
| | Wound infection | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| Musculoskeletal and connective tissue disorders | Pain in extremity | 1 | 1 (0.95%) | 1 | 1 (1.22%) | 2 | 2 (1.29%) |
| | Sciatica | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| Renal and urinary disorders | Pollakiuria | 0 | 0 (0.00%) | 1 | 1 (1.22%) | 1 | 1 (0.65%) |
| | Urinary incontinence | 0 | 0 (0.00%) | 1 | 1 (1.22%) | 1 | 1 (0.65%) |
| General disorders and administration site conditions | Swelling | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |

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Programming note: Order in descending order of frequency by SOC and then descending order by PT.

**Note:** This table includes all AEs including those categorised as serious, if only the non-serious AEs are required then the number of events for and number of patients should be reduced by 1 for the following adverse events: Injury, poisoning and procedural complications / Surgical procedure repeated, Nervous system disorders / Peroneal nerve palsy, Infections and infestations / Postoperative wound infection, Injury, poisoning and procedural complications / Pseudomeningocele. The total patients affected by AEs in this case would be 14 in the surgery arm and 3 in the TFESI arm.

**Table 6-10 Adverse events by severity**

| Adverse event | | | Surgery (n=105) | | Injection (n=82) | | Overall (n=155) | |
|---|---|---|---|---|---|---|---|---|
| **System organ class (SOC)** | **Preferred term (PT)** | **Severity** | **Events: n** | **Patients: n(%)** | **Events: n** | **Patients: n(%)** | **Events: n** | **Patients: n(%)** |
| **Total** | | **Mild** | **10** | **9 (8.67%)** | **2** | **2 (2.44%)** | **12** | **11 (7.10%)** |
| | | **Moderate** | **5** | **3 (2.86%)** | **6** | **1 (1.22%)** | **11** | **4 (2.58%)** |
| | | **Severe** | **3** | **3 (2.86%)** | **0** | **0 (0.00%)** | **3** | **3 (1.94%)** |
| Nervous system disorders | Hypoaesthesia | Mild | 1 | 1 (0.95%) | 1 | 1 (1.22%) | 2 | 2 (1.29%) |
| | | Moderate | 0 | 0 (0.00%) | 4 | 1 (1.22%) | 4 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Cerebrospinal fluid leakage | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Peroneal nerve palsy | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Radicular pain | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| Injury, poisoning and procedural complications | Dural tear | Mild | 3 | 3 (2.86%) | 0 | 0 (0.00%) | 3 | 3 (1.94%) |
| | | Moderate | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Pseudomeningocele | Mild | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Moderate | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Surgical procedure repeated | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Wound complication | Mild | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| Infections and infestations | Postoperative wound infection | Mild | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | Wound infection | Mild | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| Musculoskeletal and connective tissue disorders | Pain in extremity | Mild | 1 | 1 (0.95%) | 1 | 1 (1.22%) | 2 | 2 (1.29%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Sciatica | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| Renal and urinary disorders | Pollakiuria | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 0 | 0 (0.00%) | 1 | 1 (1.22%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | Urinary incontinence | Mild | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Moderate | 0 | 0 (0.00%) | 1 | 1 (1.22%) | 1 | 1 (0.65%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| General disorders and administration site conditions | Swelling | Mild | 1 | 1 (0.95%) | 0 | 0 (0.00%) | 1 | 1 (0.65%) |
| | | Moderate | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |
| | | Severe | 0 | 0 (0.00%) | 0 | 0 (0.00%) | 0 | 0 (0.00%) |

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Programming note: Order in descending order of frequency overall per event and then by ascending severity within event.

**Table 6-11 Line listings of adverse events by causality**

| Patient No. | System Organ Class | Preferred Term | Surgery | TFESI | | |
|---|---|---|---|---|---|---|
| | | | | Injection | Steroid | Anaesthetic |
| 1 | Musculoskeletal and connective tissue disorders | Sciatica | Almost certainly | | | |
| 2 | Infections and infestations | Wound infection | Almost certainly | | | |
| 2 | Injury, poisoning and procedural complications | Surgical procedure repeated | Almost certainly | | | |
| 3 | Nervous system disorders | Hypoaesthesia | Probably | | | |
| 4 | Infections and infestations | Postoperative wound infection | Almost certainly | | | |
| 5 | Injury, poisoning and procedural complications | Dural tear | Almost certainly | | | |
| 6 | Nervous system disorders | Hypoaesthesia | | Possibly | | |
| 6 | Nervous system disorders | Hypoaesthesia | | Possibly | | |
| 6 | Nervous system disorders | Hypoaesthesia | | Possibly | | |
| 6 | Nervous system disorders | Hypoaesthesia | | Possibly | | |
| 6 | Renal and urinary disorders | Pollakiuria | | Possibly | | |
| 6 | Renal and urinary disorders | Urinary incontinence | | Possibly | | Possibly |
| 7 | Musculoskeletal and connective tissue disorders | Pain in extremity | | Almost certainly | Possibly | Possibly |
| 8 | General disorders and administration site conditions | Swelling | Almost certainly | | | |
| 9 | Musculoskeletal and connective tissue disorders | Pain in extremity | Probably | | | |
| 10 | Injury, poisoning and procedural complications | Wound complication | Probably | | | |
| 11 | Injury, poisoning and procedural complications | Dural tear | Almost certainly | | | |
| 12 | Nervous system disorders | Peroneal nerve palsy | Almost certainly | | | |
| 13 | Injury, poisoning and procedural complications | Pseudomeningocele | Almost certainly | | | |
| 14 | Nervous system disorders | Hypoaesthesia | | Probably | Probably | Probably |
| 15 | Infections and infestations | Postoperative wound infection | Almost certainly | | | |
| 15 | Nervous system disorders | Radicular pain | Almost certainly | | | |
| 16 | Injury, poisoning and procedural complications | Dural tear | Almost certainly | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 17 | Injury, poisoning and procedural complications | Pseudomeningocele | Almost certainly | | | |
| 17 | Nervous system disorders | Cerebrospinal fluid leakage | Almost certainly | | | |
| 18 | Injury, poisoning and procedural complications | Dural tear | Almost certainly | | | |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\06B-Safety Tables.SAS*

### 6.7.2 Serious adverse events

**Table 6-12 SAE line listings**

| Allocation | System Organ Class (SOC) / Preferred Term (PT) | Onset Date | Serious Criteria | | Severity | Expected | Related | Action | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | PI | CI | PI | CI | PI / CI | | |
| Surgical Microdiscectomy | Injury, poisoning and procedural complications / Surgical procedure repeated | 25/11/2015 | Required Hospitalisation | Required Hospitalisation | Severe | Expected | Almost certainly / Almost certainly | Hospital admission, Other action: Redo disc surgery | Resolved |
| Surgical Microdiscectomy | Nervous system disorders / Peroneal nerve palsy | 11/02/2017 | Prolonged existing hospitalisation | Prolonged existing hospitalisation, Persistent or significant disability / incapacity, weakness of foot, further surgical intervention. | Severe | Expected | Almost certainly / Almost certainly | Treated with concomitant medication, Prolongation of hospital stay, Other action: Return to theatre. re-explored surgically 12/02/2017 | Ongoing at final follow up |
| Surgical Microdiscectomy | Infections and infestations / Postoperative wound infection | 19/09/2017 | Required Hospitalisation | Required Hospitalisation | Severe | Expected | Almost certainly/ Probably | Treated with concomitant medication, Hospital admission | Resolved |

| Allocation | System Organ Class (SOC) / Preferred Term (PT) | Onset Date | Serious Criteria | | Severity | Expected | Related | Action | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | PI | CI | PI | CI | PI / CI | | |
| Surgical Microdiscectomy | Injury, poisoning and procedural complications / Pseudomeningocele | 05/12/2016 | Required Hospitalisation | Required Hospitalisation | Moderate | Expected | Almost certainly/ Almost certainly | Treated with concomitant medication, Hospital admission, Other action: MRI. since follow-up report 1 patient has attended 2 outpatient appointments in the neurosurgery dept. Attended outpatient appts in Neurosurgery Dept | Resolved |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\06B-Safety Tables.SAS*

## 6.8 Efficacy data

### 6.8.1 Primary efficacy assessment

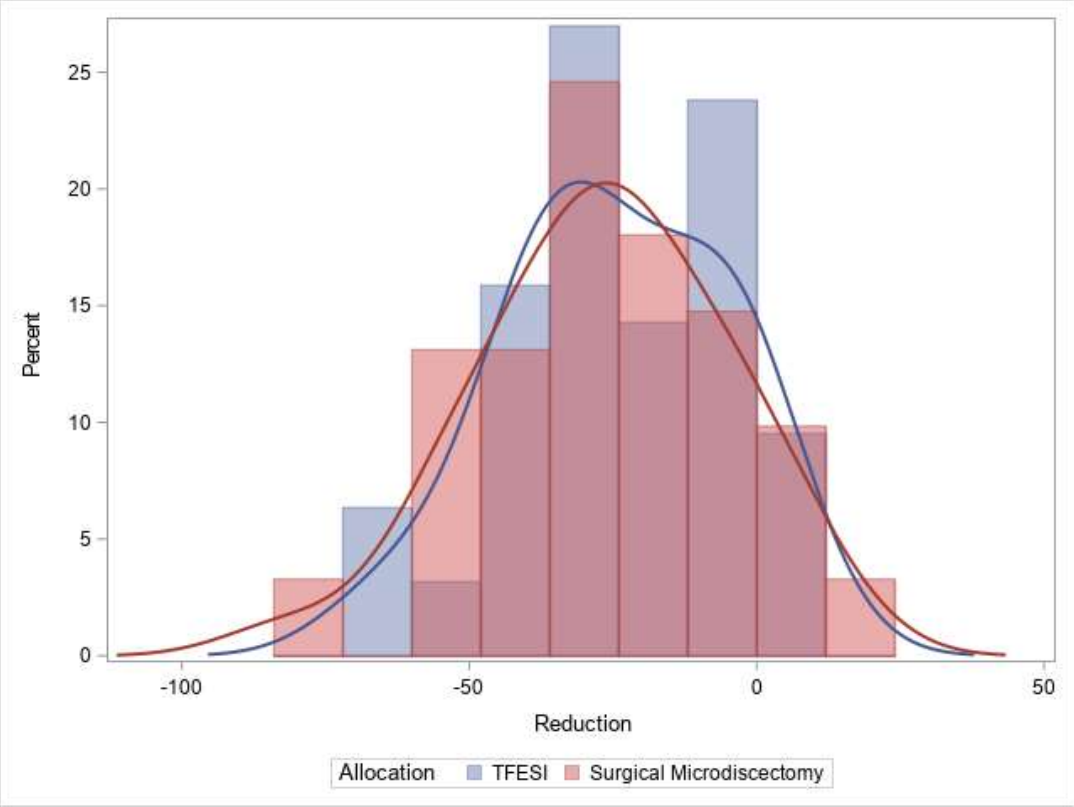
#### 6.8.1.1 ODQ (18 weeks)

**Table 6-13 ODQ summaries at baseline and week 18**

| Time point | Summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Baseline | **N** | **83** | **79** | **162** |
| | N missing | 0 | 1 | 1 |
| | Mean (S.D.) | 49.39 (17.81) | 53.74 (19.35) | 51.51 (18.64) |
| | Median (IQR) | 46.67 (36.00,62.22) | 54.00 (40.00,71.11) | 50.00 (38.00,66.00) |
| Week 18 | **N** | **61** | **63** | **124** |
| | N missing / invalid | 22 | 17 | 39 |
| | Mean (S.D.) | 22.30 (19.83) | 30.02 (24.38) | 26.22 (22.51) |
| | Median (IQR) | 18.00 (6.00,36.00) | 22.22 (10.00,50.00) | 20.00 (9.00,37.89) |
| Difference | **N** | 61 | 63 | 124 |
| | N missing/ invalid | 22 | 17 | 39 |
| | Mean (S.D.) | -26.74 (21.35) | -24.52 (18.89) | -25.61 (20.09) |
| | Median (IQR) | -26 (-40,-8.89) | -26 (-38,-6) | -26 (-39,-8) |
| | 95% CI | (-32.21 , -21.27) | (-29.28 , -19.76) | (-29.18 , -22.04) |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

**Figure 6-1 Distribution of the differences the in baseline and week 18 ODQ scores**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

For the patients who completed a valid baseline and week 18 ODQ questionnaire within the correct window, the following table shows a breakdown of the number of participants who improved or got worse in each treatment arm.

**Table 6-14 Frequencies of level of improvement for the ODQ scores**

| Change in symptoms | Surgery n=61 | Injection n=63 | Overall n=124 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Clinically significant improvement*** | 45 (73.8%) | 43 (68.3%) | 88 (71.0%) |
| **Small improvement** | 8 (13.1%) | 14 (22.2%) | 22 (17.7%) |
| **Symptoms got worse** | 8 (13.1%) | 6 (9.5%) | 14 (11.3%) |

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***Note:** A reduction of 10 points for the ODQ score was considered clinically important.

**Table 6-15 Model estimates for ODQ**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | -4.37 | (-17.03 , 8.28) | - |
| ODQ at baseline | 0.63 | (0.45 , 0.81) | - |
| Surgery versus Injection | -4.25 | (-11.09 , 2.59) | 0.221 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

### 6.8.1.2 ODQ estimates when patients switched treatment arms

The approach to primary outcome analysis was ITT, there were some treatment cross-overs before primary outcome time point. Below are summary statistics for the patients who did switch treatments (before completion of valid primary outcome) and those who did not have a cross-over before PO completion.

**Table 6-16 Summary statistics for ODQ by cross-over status**

| Crossover before PO | No | | | | Yes | | | |
|---|---|---|---|---|---|---|---|---|
| Initial treatment actually received | Surgery | | Injection | | Surgery | | Injection | |
| ODQ time point | BL | 18 | BL | 18 | BL | 18 | BL | 18 |
| N | 57 | 57 | 47 | 47 | 1 | 1 | 14 | 14 |
| Mean | 49.84 | 21.58 | 50.58 | 27.74 | 52 | 44 | 64.17 | 35.24 |
| Std. Dev. | 18.58 | 19.81 | 19.77 | 24.23 | . | . | 14.97 | 23.15 |
| Median | 44 | 18 | 48.89 | 20 | 52 | 44 | 67 | 24 |
| LQ | 36 | 6 | 36 | 8 | 52 | 44 | 56 | 20 |
| UQ | 62 | 35.56 | 66 | 44 | 52 | 44 | 72 | 54 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\07A-FU TC.sas*

#### 6.8.1.3 ODQ sensitivity analysis

As the amount of missing data was found to be >10% a sensitivity analysis was conducted to test the robustness of our primary analysis by using multiple imputations to impute missing ODQ questionnaire scores. Out of the 163 randomised patients 39 (23.93 %) were excluded from primary outcome analysis so this exceeds the 10% missing data criteria. Of the 39 exclusions 22/83 (26.51%) were in the surgery arm and 17/80 (21.25%) were in the injection arm.

162 patients were included in the sensitivity analysis, 1 patient in the TFESI arm was still excluded as they did not have a baseline ODQ so a week 18 questionnaire could not be imputed for this patient.

**Table 6-17 Model estimates for ODQ with imputed data**

| **Original parameter estimates** | **Parameter Estimate** | **Confidence interval** | ***p*-value** |
|---|---|---|---|
| Intercept | -4.37 | (-17.03 , 8.28) | - |
| ODQ at baseline | 0.63 | (0.45 , 0.81) | - |
| Surgery versus Injection | -4.25 | (-11.09 , 2.59) | 0.221 |
| **Imputed parameter estimates** | **Parameter Estimate** | **Confidence interval** | ***p*-value** |
| Intercept | 3.12 | (-14.63 , 8.40) | - |
| ODQ at baseline | 0.67 | (0.48 , 0.86) | - |
| Surgery versus Injection | -3.08 | (-10.16 , 3.99) | 0.393 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03F-Primary Outcome - sensitvity.sas*

#### 6.8.1.4 Extended ODQ model

There were 56 participants in the Surgery arm and 53 in the injection arm for this analysis.

**Table 6-18 Model estimates for the extended primary outcome mixed effects model**

| **Variable** | **Level** | **Estimate** | **CI** | **p-value** |
|---|---|---|---|---|
| Intercept | | 3.40 | (-29.36,36.17) | - |
| Baseline ODQ | | 0.62 | (0.42,0.82) | - |
| Age (years) | | -0.16 | (-0.56,0.23) | - |
| Gender | Female | 7.70 | (0.05,15.34) | - |
| | Male | 0 | . | - |
| Duration of Symptoms (weeks) | | 0.1667 | (-0.26,0.59) | - |
| BMI ($KG/M^2$) | | -0.2591 | (-0.90,0.39) | - |
| Volume | Between 25%-50% | -0.1854 | (-7.85,7.48) | - |
| | Greater than 50% | -10.7563 | (-31.03,9.52) | - |
| | Less than 25% | 0 | . | - |
| Allocation | Surgery Vs Injection | -5.0334 | (-12.76,2.70) | 0.1991 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

#### 6.8.1.5 Post-hoc analysis: Extended model including level of disc prolapse

There were 54 participants in the Surgery arm and 52 in the injection arm for this analysis.

**Table 6-19 Parameter estimates for extended model included disc prolapse level**

| Variable | Level | Estimate | CI | p-value |
|---|---|---|---|---|
| Intercept | | 5.95 | (-28.76,40.66) | - |
| Baseline ODQ | | 0.63 | (0.43,0.83) | - |
| Age (years) | | -0.2 | (-0.61,0.21) | - |
| Gender | Female | 5.78 | (-2.06,13.63) | - |
| | Male | 0 | - | - |
| Duration of Symptoms (weeks) | | 0.22 | (-0.21,0.65) | - |
| BMI ($KG/M^2$) | | -0.22 | (-0.88,0.45) | - |
| Location | L2/3 | -17.07 | (-56.93,22.79) | |
| | L3/4 | 13.81 | (-25.93,53.55) | |
| | L4/5 | -5.6 | (-13.48,2.29) | |
| | L5/S1 | 0 | - | - |
| Volume | Between 25%-50% | -17.07 | (-8.68,7.04) | - |
| | Greater than 50% | 13.81 | (-32.05,8.36) | - |
| | Less than 25% | 0 | - | - |
| Allocation | Surgery Vs Injection | -4.94 | (-12.81,2.93) | 0.215 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

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

#### 6.8.2.1 Longitudinal analysis

Change from baseline summaries (ODQ score at follow up - baseline) are presented below were 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).

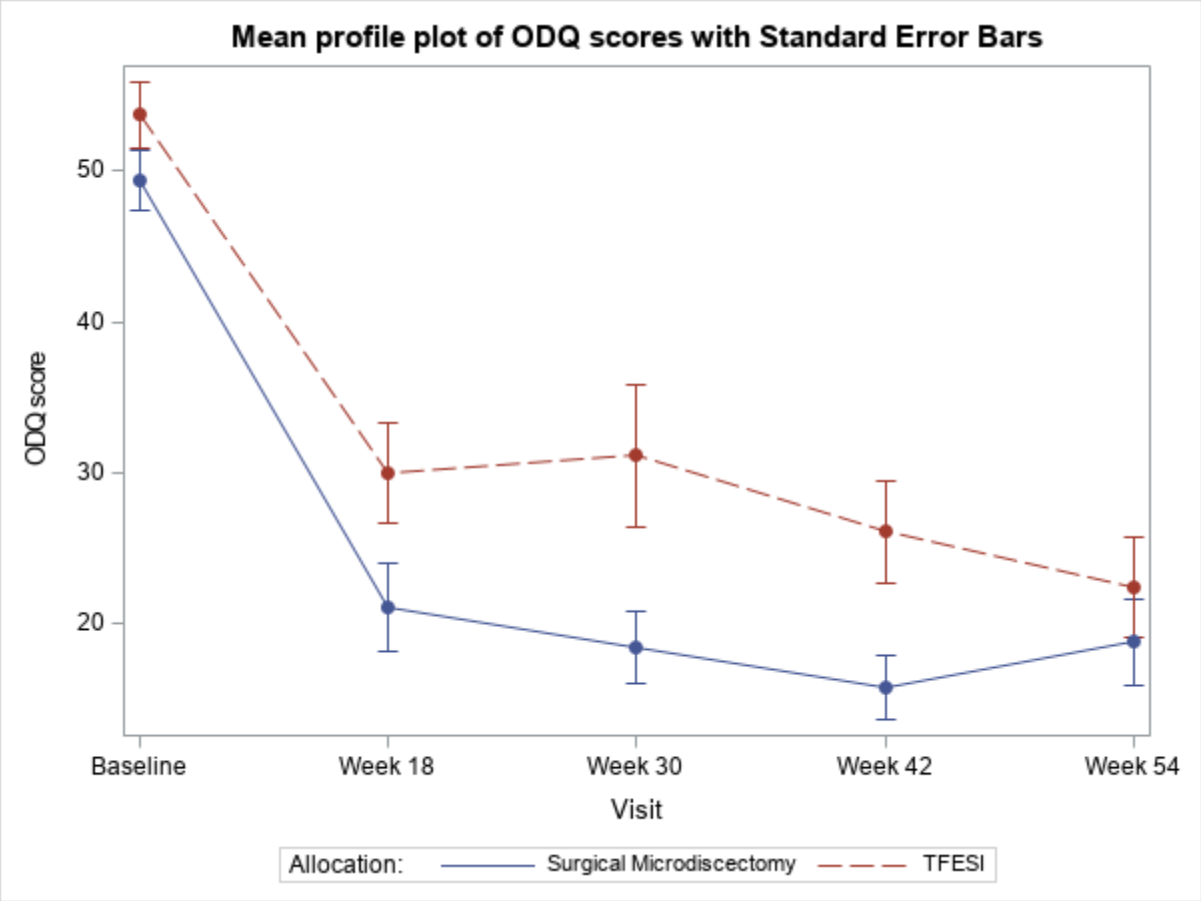
The ODQ is only considered valid if at least 8 out of 10 items were answered.

**Table 6-20 Change from baseline summaries for ODQ**

| Time point | summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Week 18 ODQ summary | **N** | **46** | **51** | **97** |
| | Mean (S.D.) | -27.18 (22.31) | -24.29 (18.28) | -25.66 (20.24) |
| | Median (IQR) | -27.00 (-40.00--8.89) | -26.00 (-36.00--8.00) | -26.00 (-38.00--8.00) |
| | Range | -84.00 - 16.00 | -65.11 - 10.00 | -84.00 - 16.00 |
| | N out of window | 22 | 15 | 37 |
| | N invalid | 1 | 0 | 1 |
| | N missing | 14 | 14 | 28 |
| Week 30 ODQ summary | **N** | **40** | **30** | **70** |
| | Mean (S.D.) | -26.62 (19.12) | -23.25 (17.45) | -25.17 (18.37) |
| | Median (IQR) | -29.00 (-33.67--13.00) | -25.33 (-34.00--10.00) | -27.33 (-34.00--12.00) |
| | Range | -78.00 - 12.00 | -64.00 - 12.00 | -78.00 - 12.00 |
| | N out of window | 12 | 14 | 26 |
| | N invalid | 0 | 1 | 1 |
| | N missing | 31 | 35 | 66 |
| Week 42 ODQ summary | **N** | **40** | **34** | **74** |
| | Mean (S.D.) | -31.40 (17.22) | -25.51 (23.74) | -28.69 (20.54) |
| | Median (IQR) | -30.00 (-41.00--20.39) | -26.00 (-42.00--8.00) | -29.00 (-42.00--16.00) |
| | Range | -68.00 - 14.00 | -70.00 - 21.11 | -70.00 - 21.11 |
| | N out of window | 10 | 11 | 21 |
| | N invalid | 1 | 0 | 1 |
| | N missing | 32 | 35 | 67 |
| Week 54 ODQ summary | **N** | **48** | **42** | **90** |
| | Mean (S.D.) | -30.38 (17.77) | -31.10 (24.35) | -30.71 (20.97) |
| | Median (IQR) | -31.00 (-42.00--20.00) | -23.00 (-48.00--12.00) | -29.00 (-42.00--18.00) |
| | Range | -68.00 - 9.56 | -84.00 - 4.00 | -84.00 - 9.56 |
| | N out of window | 16 | 17 | 33 |
| | N invalid | 0 | 0 | 0 |
| | N missing | 19 | 21 | 40 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

**Figure 6-2 Profile plots of ODQ scores**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

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. As such there were 75 patients in the surgery arm and 72 patients in the TFESI arm included in this analysis.

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.

**Table 6-21 Parameter estimates for ODQ longitudinal model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 1.17 | (-9.87,12.22) | - |
| Baseline ODQ | 0.57 | (0.41,0.73) | - |
| Time (Weeks) | -0.08 | (-0.15,-0.02) | - |
| Surgery versus Injection | -4.67 | (-10.61,1.28) | 0.123 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

#### 6.8.2.2 Post-hoc analysis

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).

**Table 6-22 Post-hoc: parameter estimates for ODQ joint model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 2.65 | (-7.76, 11.26) | - |
| Baseline ODQ | 0.54 | (0.37, 0.73) | - |
| Time (Weeks) | -0.08 | (-0.16, -0.02) | - |
| Surgery versus Injection | -4.62 | (-9.84, 1.27) | 0.108 |

*R file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 2.0\SAS Programmes\Joint modelling.R*

The parameter estimates are similar to the original longitudinal estimates found in Table 6-21 and the conclusions remain unchanged once adjusted for informative dropout.

To consider the effects of baseline dropout (as these would not include in the original model or the joint model due to lack of follow up), the following summaries are provided.

**Table 6-23 Post-hoc: summaries of baseline ODQ scores by dropout status**

| | N | Mean (SD) | Median (IQR) | Range |
|---|---|---|---|---|
| Overall baseline ODQ for surgical arm | 83 | 49.39 (17.81) | 46.67 (36 - 62.22) | 14 - 96 |
| Overall baseline ODQ for TFESI arm | 79 | 53.74 (19.35) | 54 (40 - 71.11) | 18 - 100 |
| **Baseline ODQ for baseline dropout surgical arm** | **7** | **45.78 (23.02)** | **38 (28 - 64.44)** | **18 - 86** |
| **BL ODQ for BL dropout TFESI arm** | **7** | **57.43 (23.17)** | **56 (44 - 80)** | **20 - 82** |
| Baseline ODQ for no dropout/ non-baseline dropout in surgical arm | 76 | 49.72 (17.41) | 46.67 (36 - 62.11) | 14 - 96 |
| Baseline ODQ for no dropout/ non-baseline dropout in TFESI arm | 72 | 53.38 (19.09) | 53 (39 - 70.56) | 18 - 100 |

For the participants who dropped out at baseline, the mean and median ODQ scores are not the same between treatment groups. They are lower in the group randomised to surgical microdiscectomy. However, since these groups are small, no formal comparison has been made.

### 6.8.3 Secondary efficacy endpoint 2 – Leg pain (18, 30, 42 and 54 weeks)

#### 6.8.3.1 Longitudinal analysis

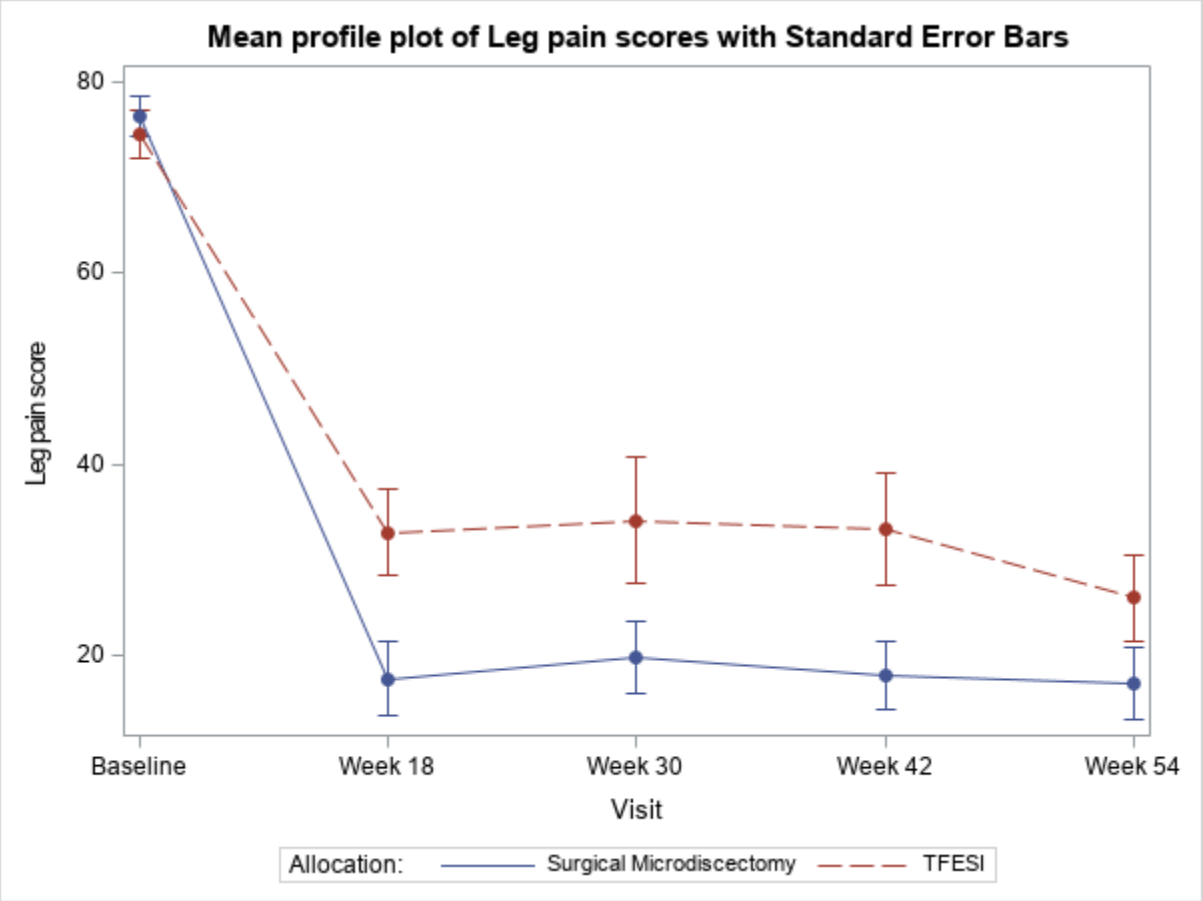
Change from baseline summaries (Numerical rating of leg pain at follow up - baseline) are presented below were the numerical rating for leg pain were completed. A lower leg pain rating (0-100) represents lower overall pain so a decrease from baseline represents an improvement. Questionnaires were only 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).

**Table 6-24 Change from baseline summaries for leg pain rating**

| Time point | summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Week 18 leg pain summary | **N** | **45** | **49** | **94** |
| | Mean (S.D.) | -58.31 (34.51) | -43.55 (32.52) | -50.62 (34.12) |
| | Median (IQR) | -65.00 (-85.00--40.00) | -50.00 (-75.00--20.00) | -60.00 (-80.00--25.00) |
| | Range | -100.00 - 20.00 | -95.00 - 25.00 | -100.00 - 25.00 |
| | N out of window | 16 | 14 | 30 |
| | N missing | 22 | 17 | 39 |
| Week 30 leg pain summary | **N** | **38** | **30** | **68** |
| | Mean (S.D.) | -54.37 (27.05) | -42.70 (35.27) | -49.22 (31.25) |
| | Median (IQR) | -60.00 (-70.00--40.00) | -42.50 (-80.00--10.00) | -55.00 (-75.00--20.00) |
| | Range | -100.00 - 5.00 | -95.00 - 15.00 | -100.00 - 15.00 |
| | N out of window | 10 | 12 | 22 |
| | N missing | 35 | 38 | 73 |
| Week 42 leg pain summary | **N** | **37** | **33** | **70** |
| | Mean (S.D.) | -55.81 (31.66) | -47.12 (42.28) | -51.71 (37.03) |
| | Median (IQR) | -70.00 (-80.00--30.00) | -49.00 (-85.00--25.00) | -65.00 (-80.00--30.00) |
| | Range | -100.00 - 30.00 | -100.00 - 45.00 | -100.00 - 45.00 |
| | N out of window | 9 | 11 | 20 |
| | N missing | 37 | 36 | 73 |
| Week 54 leg pain summary | **N** | **43** | **39** | **82** |
| | Mean (S.D.) | -55.44 (33.57) | -47.08 (33.06) | -51.46 (33.39) |
| | Median (IQR) | -65.00 (-80.00--30.00) | -50.00 (-74.00--25.00) | -57.50 (-80.00--30.00) |
| | Range | -100.00 - 19.00 | -100.00 - 40.00 | -100.00 - 40.00 |
| | N out of window | 15 | 17 | 32 |
| | N missing | 25 | 24 | 49 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

**Figure 6-3 Profile plots of leg pain rating**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

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. As such there were 70 patients in the surgery arm and 70 patients in the TFESI arm included in this analysis.

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.

**Table 6-25 Parameter estimates for leg pain rating longitudinal model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 27.95 | (6.43 , 49.48) | - |
| Baseline leg pain | 0.12 | (-0.09 , 0.33) | - |
| Time (Weeks) | -0.08 | (-0.19 , 0.04) | - |
| Surgery versus Injection | -7.04 | (-15.81 , 1.73) | 0.115 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

**Table 6-26 Summary statistics for leg pain rating by cross-over status**

| Crossover before Week 18 questionnaire | No | | | | Yes | | | |
|---|---|---|---|---|---|---|---|---|
| **Initial treatment actually received** | **Surgery** | | **Injection** | | **Surgery** | | **Injection** | |
| **Leg pain time point** | **BL** | **18** | **BL** | **18** | **BL** | **18** | **BL** | **18** |
| **N** | 57 | 57 | 47 | 47 | 60 | 80 | 14 | 14 |
| **Mean** | 76.46 | 19.84 | 70.6 | 32.34 | . | . | 86.43 | 29.29 |
| **Std. Dev.** | 19.94 | 26.58 | 21.91 | 31.99 | 60 | 80 | 17.26 | 26.52 |
| **Median** | 80 | 10 | 75 | 20 | 60 | 80 | 90 | 20 |
| **LQ** | 65 | 0 | 50 | 5 | 60 | 80 | 80 | 10 |
| **UQ** | 90 | 30 | 90 | 60 | 60 | 80 | 100 | 55 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

#### 6.8.3.2 Post-hoc analysis

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 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.

**Table 6-27 Post-hoc: parameter estimates for leg pain joint model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 24.86 | (9.91, 41.09) | |
| Baseline leg pain | 0.12 | (-0.09, 0.29) | |
| Time (Weeks) | -0.06 | (-0.18, 0.04) | |
| Surgery versus Injection | -7.06 | (-15.82, 0.86) | 0.098 |

*R file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 2.0\SAS Programmes\Joint modelling.R*

The parameter estimates are similar to the original longitudinal estimates found in Table 6-25 and the conclusions remain unchanged once adjusted for informative dropout.

### 6.8.4 Secondary efficacy endpoint 3 – Back pain (18, 30, 42 and 54 weeks)

#### 6.8.4.1 Longitudinal analysis

Change from baseline summaries (Numerical rating of back pain at follow up - baseline) are presented below were 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).

**Table 6-28 Change from baseline summaries for back pain rating**

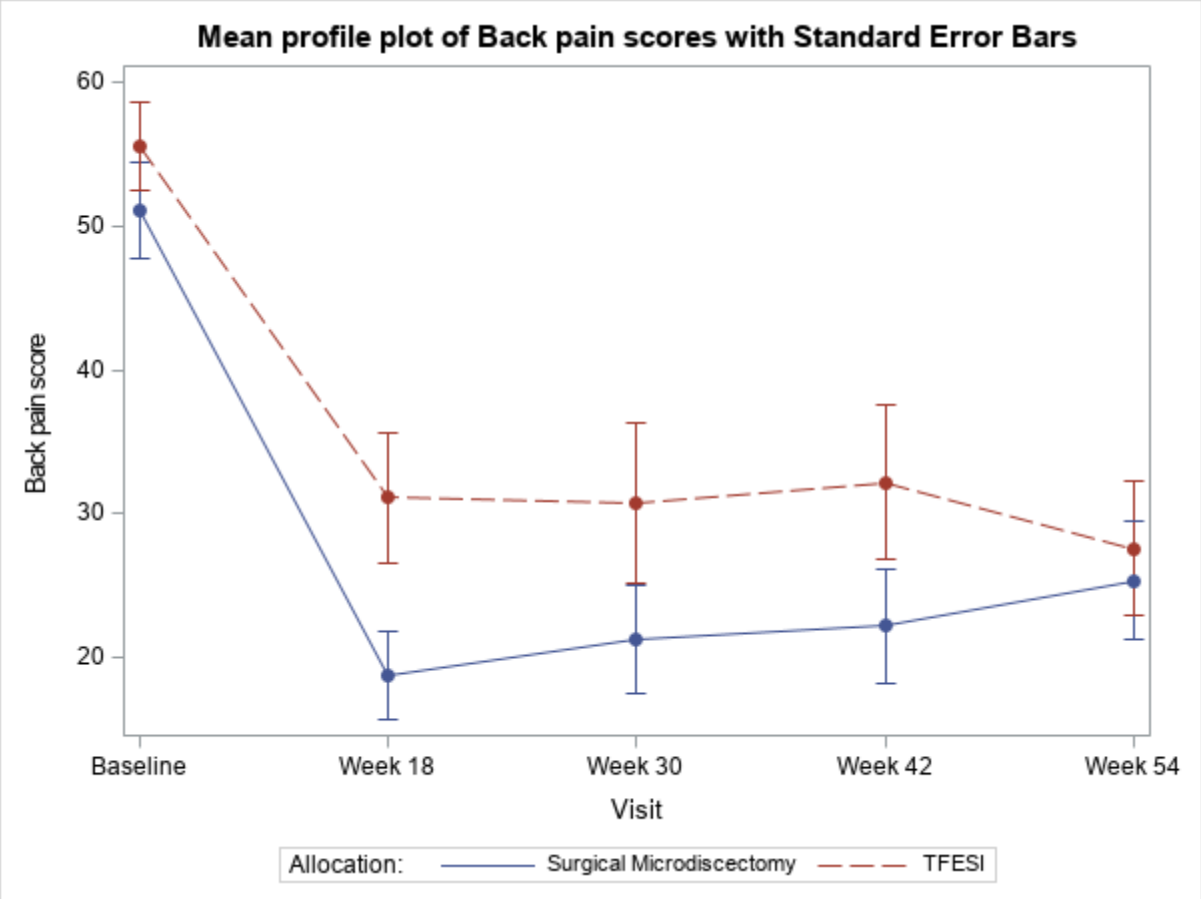
| Time point | summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Week 18 back pain summary | **N** | 45 | 49 | 94 |
| | Mean (S.D.) | -26.02 (32.83) | -23.41 (27.69) | -24.66 (30.12) |
| | Median (IQR) | -22.00 (-55.00-0.00) | -18.00 (-45.00-0.00) | -20.00 (-52.00-0.00) |
| | Range | -95.00 - 45.00 | -84.00 - 16.00 | -95.00 - 45.00 |
| | N out of window | 16 | 14 | 30 |
| | N missing | 22 | 17 | 39 |
| Week 30 back pain summary | **N** | **38** | **30** | **68** |
| | Mean (S.D.) | -25.00 (32.04) | -24.33 (31.95) | -24.71 (31.77) |
| | Median (IQR) | -25.00 (-50.00-0.00) | -15.00 (-45.00-0.00) | -20.00 (-47.50-0.00) |
| | Range | -95.00 - 40.00 | -90.00 - 30.00 | -95.00 - 40.00 |
| | N out of window | 9 | 12 | 21 |
| | N missing | 36 | 38 | 74 |
| Week 42 back pain summary | **N** | **37** | **33** | **70** |
| | Mean (S.D.) | -20.81 (37.43) | -23.00 (37.29) | -21.84 (37.11) |
| | Median (IQR) | -25.00 (-45.00--1.00) | -20.00 (-50.00-0.00) | -20.00 (-49.00-0.00) |
| | Range | -95.00 - 80.00 | -84.00 - 48.00 | -95.00 - 80.00 |
| | N out of window | 9 | 11 | 20 |
| | N missing | 37 | 36 | 73 |
| Week 54 back pain summary | **N** | **42** | **39** | **81** |
| | Mean (S.D.) | -23.07 (34.54) | -22.90 (29.11) | -22.99 (31.84) |
| | Median (IQR) | -22.50 (-55.00-0.00) | -15.00 (-45.00-0.00) | -20.00 (-48.00-0.00) |
| | Range | -95.00 - 65.00 | -80.00 - 30.00 | -95.00 - 65.00 |
| | N out of window | 16 | 17 | 33 |
| | N missing | 25 | 24 | 49 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

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. As such there were 71 patients in the surgery arm and 70 patients in the TFESI arm included in this analysis.

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.

**Figure 6-4 Profile plots of back pain rating**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

**Table 6-29 Parameter estimates for back pain rating longitudinal model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 9.12 | (-2.72 , 20.98) | - |
| Baseline back pain | 0.39 | (0.24 , 0.54) | - |
| Time (Weeks) | 0.08 | (-0.03 , 0.18) | - |
| Surgery versus Injection | -3.01 | (-11.29 , 5.26) | 0.473 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

**Table 6-30 Summary statistics for back pain rating by cross-over status**

| **Crossover before Week 18 questionnaire** | **No** | | | | **Yes** | | | |
|---|---|---|---|---|---|---|---|---|
| **Initial treatment actually received** | **Surgery** | | **Injection** | | **Surgery** | | **Injection** | |
| **Leg pain time point** | **BL** | **18** | **BL** | **18** | **BL** | **18** | **BL** | **18** |
| **N** | 57 | 57 | 47 | 47 | 55 | 2 | 47.14 | 29 |
| **Mean** | 47.79 | 21.53 | 54.09 | 32.28 | . | . | 32.8 | 28.43 |
| **Std. Dev.** | 28 | 24.47 | 28.1 | 32.76 | 55 | 2 | 50 | 16.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Median** | 50 | 10 | 60 | 20 | 55 | 2 | 10 | 5 |
| **LQ** | 30 | 5 | 30 | 5 | 55 | 2 | 75 | 60 |
| **UQ** | 70 | 25 | 75 | 60 | 55 | 2 | 47.14 | 29 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

#### 6.8.4.2 Post-hoc analysis

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).

**Table 6-31 Post-hoc: parameter estimates for back pain joint model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 8.92 | (-0.24, 16.01) | |
| Baseline back pain | 0.39 | (0.25, 0.54) | |
| Time (Weeks) | 0.08 | (-0.04, 0.21) | |
| Surgery versus Injection | -2.87 | (-10.58, 3.16) | 0.457 |

*R file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 2.0\SAS Programmes\Joint modelling.R*

The parameter estimates are similar to the original longitudinal estimates found in Table 6-29 and the conclusions remain unchanged once adjusted for informative dropout.

### 6.8.5 Secondary efficacy endpoint 4 – Likert scale for satisfaction with care

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.

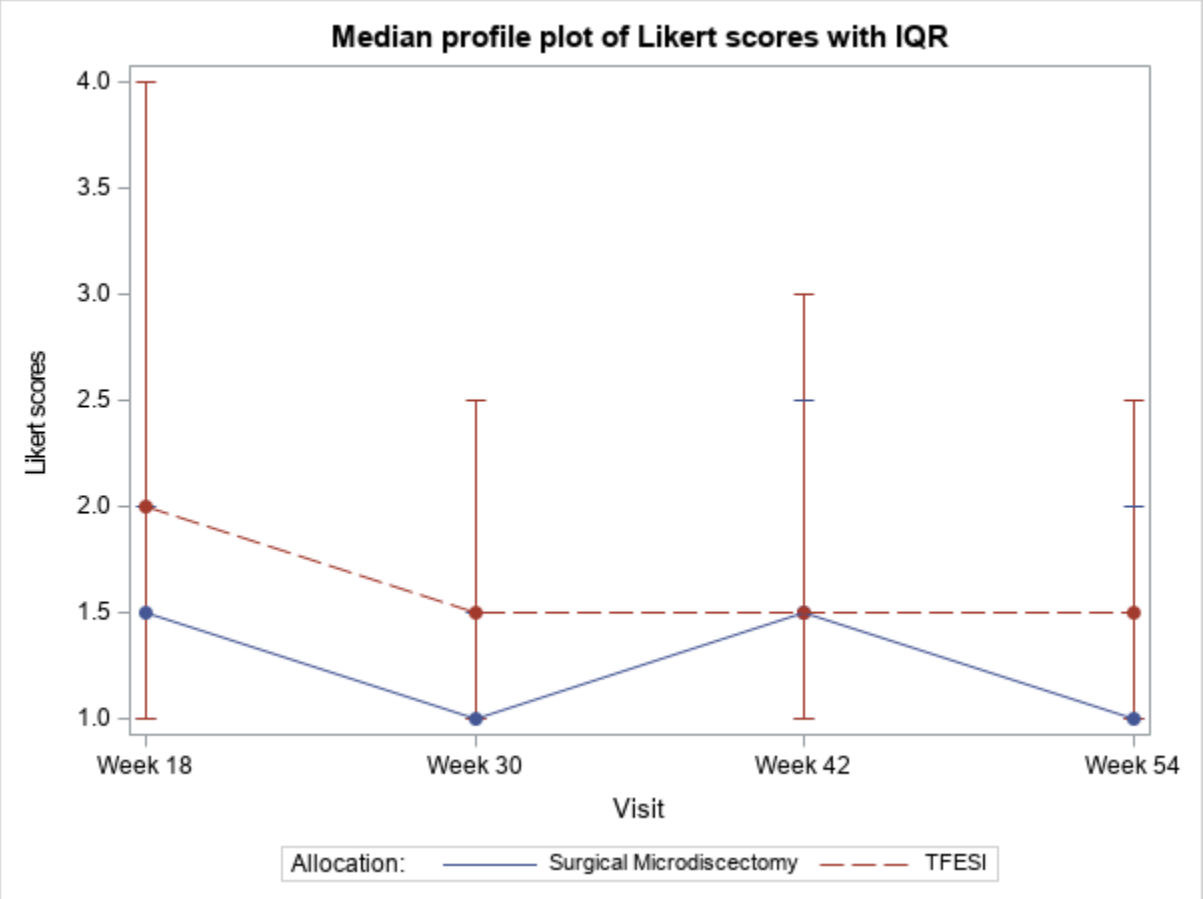
**Table 6-32 Summaries for Likert scale for satisfaction with care at week 54**

| Allocation | N | N missing | Median | Lower Quartile | Upper Quartile |
|---|---|---|---|---|---|
| Surgical Microdiscectomy | 61 | 22 | 1 | 1 | 2 |
| TFESI | 58 | 22 | 1.5 | 1 | 3 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

The median difference at 54 weeks was 0.5.

**Figure 6-5 Median profile plot for Likert score for satisfaction**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

**Table 6-33 Mann-Whitney results**

| Mann-Whitney U statistic | Z-statistic | p-value |
|---|---|---|
| 1358.5 | 2.30 | 0.021 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

### 6.8.6 Secondary efficacy endpoint 5 – Roland-Morris (18, 30, 42, 54 weeks)

#### 6.8.6.1 Longitudinal analysis

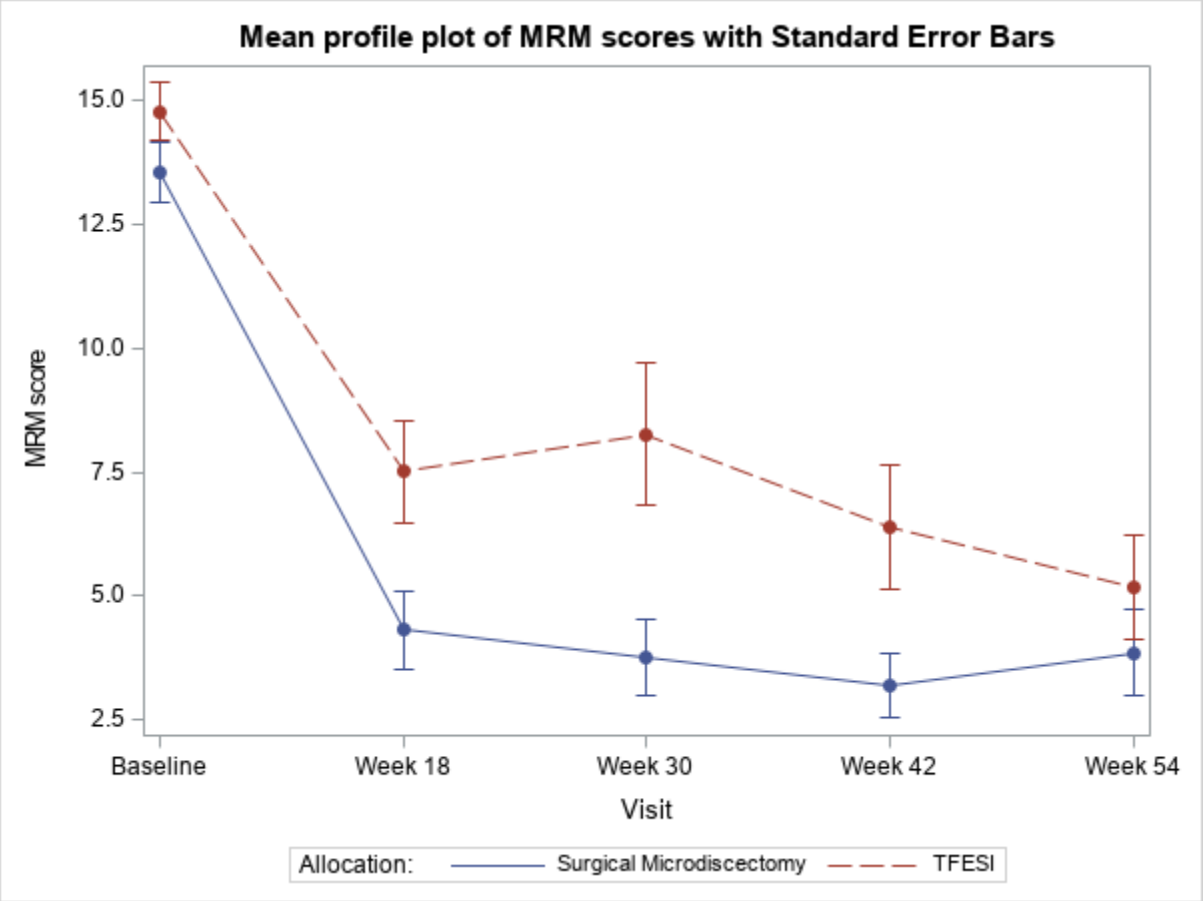
Change from baseline summaries (Roland-Morris at follow up - baseline) are presented below were the modified Roland-Morris (MRM) was completed at both time points. A Lower MRM score relates to lower levels of disability so a decrease from baseline represents an improvement. Questionnaires are only included 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).

**Table 6-34 Change from baseline summaries for MRM**

| Time point | summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Week 18 MRM summary | **N** | **47** | **51** | **98** |
| | Mean (S.D.) | -9.09 (6.27) | -7.73 (5.91) | -8.38 (6.09) |
| | Median (IQR) | -9.00 (-14.00--4.00) | -9.00 (-12.00--2.00) | -9.00 (-13.00--4.00) |
| | Range | -22.00 - 3.00 | -19.00 - 2.00 | -22.00 - 3.00 |
| | N out of window | 21 | 14 | 35 |
| | N missing | 15 | 15 | 30 |
| Week 30 MRM summary | **N** | **40** | **31** | **71** |
| | Mean (S.D.) | -9.58 (5.60) | -7.48 (6.68) | -8.66 (6.14) |
| | Median (IQR) | -11.00 (-13.00--6.00) | -7.00 (-12.00--2.00) | -10.00 (-13.00--4.00) |
| | Range | -19.00 - 2.00 | -20.00 - 4.00 | -20.00 - 4.00 |
| | N out of window | 11 | 14 | 25 |
| | N missing | 32 | 35 | 67 |
| Week 42 MRM summary | **N** | **39** | **34** | **73** |
| | Mean (S.D.) | -9.56 (5.86) | -8.35 (8.56) | -9.00 (7.21) |
| | Median (IQR) | -10.00 (-14.00--6.00) | -9.50 (-15.00--2.00) | -10.00 (-15.00--5.00) |
| | Range | -19.00 - 4.00 | -21.00 - 9.00 | -21.00 - 9.00 |
| | N out of window | 11 | 11 | 22 |
| | N missing | 33 | 35 | 68 |
| Week 54 MRM summary | **N** | **47** | **42** | **89** |
| | Mean (S.D.) | -9.74 (6.65) | -9.24 (6.68) | -9.51 (6.63) |
| | Median (IQR) | -12.00 (-14.00--6.00) | -9.50 (-13.00--5.00) | -10.00 (-14.00--5.00) |
| | Range | -22.00 - 8.00 | -21.00 - 6.00 | -22.00 - 8.00 |
| | N out of window | 15 | 17 | 32 |
| | N missing | 21 | 21 | 42 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03B-Primary Outcome.sas*

**Figure 6-6 Profile plots of modified Roland-Morris scores**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

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. As such there were 74 patients in the surgery arm and 72 patients in the TFESI arm included in this analysis.

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.

**Table 6-35 Parameter estimates for the MRM longitudinal model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | -0.46 | (-3.82 , 2.91) | - |
| Baseline MRM | 0.55 | (0.37 , 0.72) | - |
| Time (Weeks) | -0.02 | (-0.04 , 0.004) | - |
| Surgery versus Injection | -1.82 | (-3.67 , 0.03) | 0.054 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\03D-SO Roland Morris V2.0.sas*

#### 6.8.6.2 Post-hoc analysis

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.

**Table 6-36 Post-hoc: parameter estimates for MRM joint model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | -0.02 | (-2.60, 2.36) | |
| Baseline MRM | 0.51 | (0.36, 0.71) | |
| Time (Weeks) | -0.02 | (-0.04, 0.01) | |
| Surgery versus Injection | -1.72 | (-3.44, 0.10) | 0.063 |

*R file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 2.0\SAS Programmes\Joint modelling.R*

The parameter estimates are similar to the original longitudinal estimates found in Table 6-35Table 6-21 and the conclusions remain unchanged once adjusted for informative dropout.

### 6.8.7 Secondary efficacy endpoint 6 – COMI (18, 30, 42, 54 weeks)

#### 6.8.7.1 Longitudinal analysis

Change from baseline summaries (COMI at follow up – baseline COMI) are presented below were 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).

Only COMI questionnaires with all items answered will be included in the summaries below. If a COMI questionnaire is missing an item then it is recorded as missing.

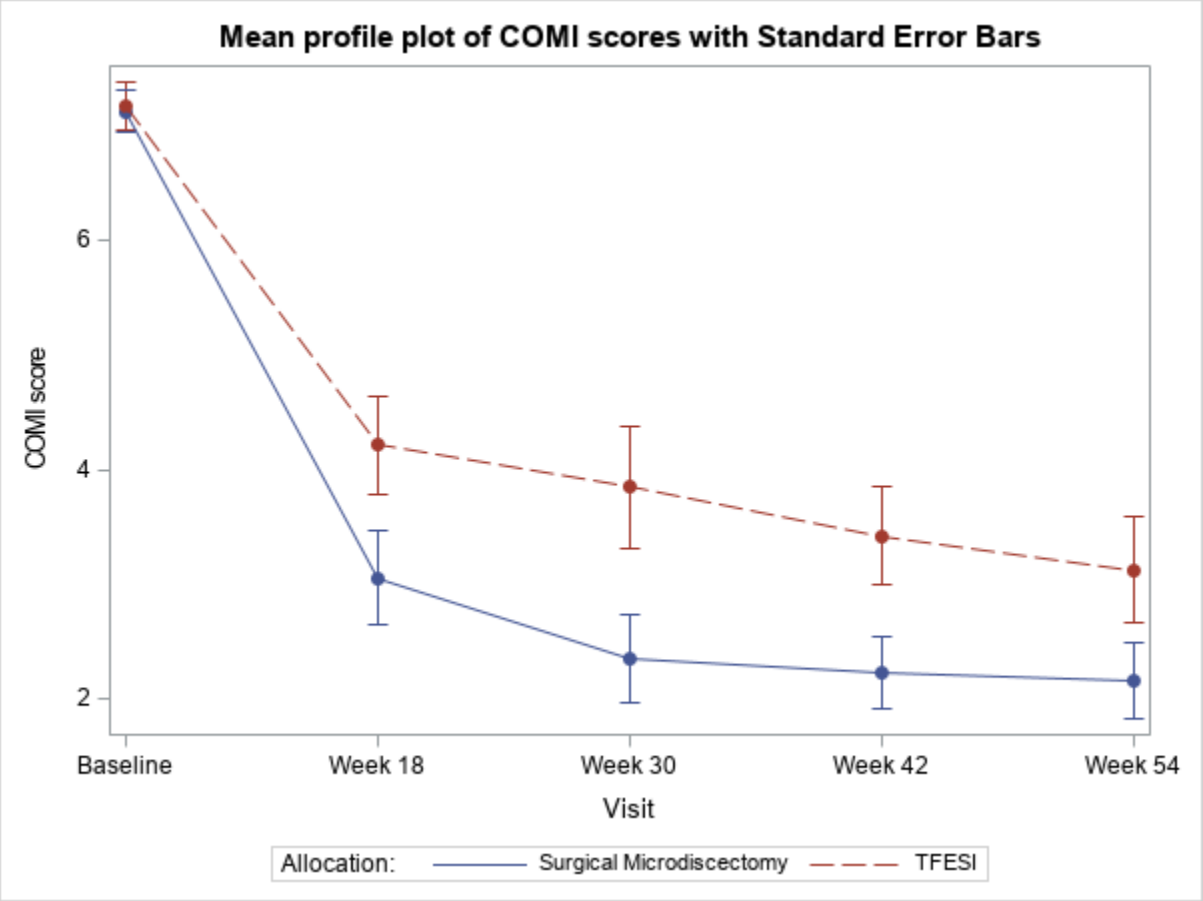
**Table 6-37 Change from baseline summaries for COMI**

| Time point | summary | Surgery | Injection | Overall |
|---|---|---|---|---|
| Week 18 COMI summary | **N** | **42** | **47** | **89** |
| | Mean (S.D.) | -3.93 (2.80) | -3.05 (2.69) | -3.46 (2.76) |
| | Median (IQR) | -4.17 (-5.83--1.67) | -3.33 (-5.00--1.25) | -3.75 (-5.42--1.25) |
| | Range | -9.17 - 1.25 | -9.17 - 1.67 | -9.17 - 1.67 |
| | N out of window | 16 | 14 | 30 |
| | N missing | 25 | 19 | 44 |
| Week 30 COMI summary | **N** | **32** | **27** | **59** |
| | Mean (S.D.) | -4.49 (2.44) | -3.33 (2.35) | -3.96 (2.45) |
| | Median (IQR) | -4.79 (-6.04--3.13) | -3.33 (-4.58--1.25) | -4.17 (-5.42--2.08) |
| | Range | -8.75 - 0.00 | -7.92 - 0.83 | -8.75 - 0.83 |
| | N out of window | 8 | 9 | 17 |
| | N missing | 43 | 44 | 87 |
| Week 42 COMI summary | **N** | **33** | **32** | **65** |
| | Mean (S.D.) | -4.92 (2.18) | -3.45 (3.14) | -4.20 (2.77) |
| | Median (IQR) | -4.58 (-6.25--4.17) | -4.58 (-5.63--1.25) | -4.58 (-5.83--3.33) |
| | Range | -8.75 - 0.00 | -8.33 - 3.33 | -8.75 - 3.33 |
| | N out of window | 8 | 6 | 14 |
| | N missing | 42 | 42 | 84 |
| Week 54 COMI summary | **N** | **39** | **37** | **76** |
| | Mean (S.D.) | -5.02 (2.32) | -3.93 (2.81) | -4.49 (2.61) |
| | Median (IQR) | -5.42 (-6.67--3.33) | -3.75 (-5.83--2.50) | -5.00 (-6.46--2.92) |
| | Range | -9.17 - 1.67 | -9.17 - 1.67 | -9.17 - 1.67 |
| | N out of window | 13 | 16 | 29 |
| | N missing | 31 | 27 | 58 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

The study design defines that COMI 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. As such there were 65 patients in the surgery arm and 67 patients in the TFESI arm included in this analysis.

**Figure 6-7 Profile plots of COMI score**




*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\08-POST HOC.sas*

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.

**Table 6-38 Parameter estimates for the COMI longitudinal model**

| Variable | Parameter Estimate | Confidence interval | *p*-value |
|---|---|---|---|
| Intercept | 0.94 | (-1.14 , 3.02) | - |
| Baseline COMI | 0.44 | (0.20 , 0.67) | - |
| Time (Weeks) | -0.02 | (-0.02 , -0.01) | - |
| Surgery versus Injection | -0.77 | (-1.58 , 0.03) | 0.059 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03C-SO COMI and Numerical rating.sas*

#### 6.8.7.2 Post-hoc analysis

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.

**Table 6-39 Post-hoc: parameter estimates for COMI joint model**

| **Variable** | **Parameter Estimate** | **Confidence interval** | ***p*-value** |
|---|---|---|---|
| Intercept | 1.45 | (-0.37, 3.16) | |
| Baseline COMI | 0.39 | (0.15, 0.66) | |
| Time (Weeks) | -0.02 | (-0.03, -0.01) | |
| Surgery versus Injection | -0.78 | (-1.54, -0.02) | 0.046 |

*R file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 2.0\SAS Programmes\Joint modelling.R*

The parameter estimates are similar to the original longitudinal estimates found in Table 6-38 however the p-value and confidence intervals suggest a marginally significant treatment effect once adjusted for informative dropout.

### 6.8.8 Secondary efficacy endpoint 7 – Work Status

Below the number of patients that are employed/not employed at baseline, week 18 and week 54 are presented 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.

The baseline CRF asks if the patient is employed and if the patient is able to work or not if they are employed. However, on the week 18 and week 54 CRF the questions asked are if the patient is employed or not and then if they have returned to work or not since the last visit and as such it can be difficult to say for certain whether the patient was employed and able to work or not at follow up. If we are unable to tell for sure then the status at the last follow up will be carried forward were there is no clear contradiction in doing so.

**Table 6-40 Employment summaries at baseline and follow up**

| Time point | Detail | Surgery (n=83) | Injection (n=80) | Overall (n=163) |
|---|---|---|---|---|
| **Baseline** | Unemployed | 21 | 13 | 34 |
| | Employed | 62 | 66 | 128 |
| | Working | 41 | 34 | 75 |
| | Not working | 21 | 32 | 53 |
| | Missing/ can't tell | 0 | 1 | 1 |
| **Week 18** | Unemployed | 18 | 16 | 34 |
| | Employed | 54 | 53 | 107 |
| | Working | 45 | 44 | 89 |
| | Not working | 6 | 9 | 15 |
| | Missing/ can't tell | 14 | 11 | 25 |
| **Week 54** | Unemployed | 15 | 13 | 28 |
| | Employed | 49 | 44 | 80 |
| | Working | 45 | 37 | 82 |
| | Not working | 0 | 1 | 1 |
| | Missing/ can't tell | 23 | 29 | 52 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03E-SO Work Status.sas*

Due to the same reasons as above the number of days lost to work cannot be calculated accurately as in some cases it is impossible to know when someone stopped work and when someone returned. As such the number of days lost to work will not be presented.

**Table 6-41 Two way table for Chi-square test of association - week 18**

| | Employment status Week 18 | |
|---|---|---|
| **Allocation** | **Not working** | **Working** |
| **Surgery** | 6 | 45 |
| **Injection** | 9 | 44 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03E-SO Work Status.sas*

The Chi-square test statistic for the test of association is 0.57 with a corresponding p-value of 0.449. The relative risk of not working across arms (Surgery/ Injection) is 0.69 with corresponding 95% CI of (0.27 , 1.81)

**Table 6-42 Two way table for Chi-square test of association - week 54**

| | Employment status Week 54 | |
|---|---|---|
| **Allocation** | **Not working** | **Working** |
| **Surgery** | 0 | 45 |
| **Injection** | 1 | 37 |

*SAS file: T:\Nerves\Statistical Analysis\Final analysis\Analysis\Version 1.0\SAS Programmes\03E-SO Work Status.sas*

***Note:*** *The assumption of expected cell count of >5 in 80% of cells to perform is not met for the week 54 employment status.*

The Chi-square test statistic for the test of association is 1.20 with a corresponding p-value of 0.274. The relative risk of not working at 54 weeks cannot be calculate as one of the cell counts for not working is 0.

## 6.9 Additional analyses

### 6.9.1 Additional analysis 1

Additional analysis 1 was the extended model for the primary outcome and is reported in section 6.8.1.4

## 7. Plots and graphs

| Plot number | Title | Section number of data to be included | Population | x-axis/y-axis |
|---|---|---|---|---|
| Figure 6-1 | Distribution of the differences the in baseline and week 18 ODQ scores | Table 6-13 ODQ summaries at baseline and week 18 (final row) | ITT | Reduction from baseline to week 18 in ODQ (%) / Percentage |
| Figure 6-2 | Profile plots of ODQ scores | Table 6-20 Change from baseline summaries for ODQ | ITT | Visit timepoint (weeks) / ODQ score (%) |
| Figure 6-3 | Profile plots of leg pain rating | Table 6-24 Change from baseline summaries for leg pain rating | ITT | Visit timepoint (weeks) / Leg pain score (score out of 100) |
| Figure 6-4 | Profile plots of back pain rating | Table 6-28 Change from baseline summaries for back pain rating | ITT | Visit timepoint (weeks) / Back pain score (score out of 100) |
| Figure 6-5 | Median profile plot for Likert score for satisfaction | Table 6-32 Summaries for Likert scale for satisfaction with care at week 54 | ITT | Visit timepoint (weeks) / Likert score for satisfaction with care (score 2-10) |
| Figure 6-6 | Profile plots of modified Roland-Morris scores | Table 6-34 Change from baseline summaries for MRM | ITT | Visit timepoint (weeks) / MRM score (score out of 24) |
| Figure 6-7 | Profile plots of COMI score | Table 6-37 Change from baseline summaries for COMI | ITT | Visit timepoint (weeks) / COMI score (Average score) |

## Appendix 1: Mapping report contents to SAP

This report has been created following the NERVES Statistical Analysis Plan V2.0 (dated 25/06/2019).

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

| Section/subsection of SAP | Item within report | Additional details (if required) |
|---|---|---|
| 14.1. Screening, eligibility and recruitment | Table 5-1 Summary of screening logs<br>Table 5-2 Reasons for ineligibility 1<br>Table 5-3 Reason for ineligibility 2<br>Table 5-4 Reason eligible patient were not approached for consent<br>Table 5-5 Reasons for eligible patient declining to participate<br>Table 5-6 Summary of randomisation by site | |
| 14.2. Post randomisation discontinuations | Table 6-4 Withdrawals from follow up | |
| 15. Protocol Deviations | Table 6-3 Protocol deviations | |
| 17.1. Data Sets Analysed | Table 6-2 Data sets analysed | |
| 17.2. Demographic and Other Baseline Characteristics | Table 6-1 All demographic details split by allocation | Included BMI |
| 17.3. Compliance with treatment | Table 6-5 Timing of treatment<br>Table 6-6 Details for patients not receiving allocated treatment<br>Table 6-7 details of trial interventions received<br>Table 6-8 Treatment cross-over in relation to primary outcome | |
| 17.4.1 Primary Outcome / 17.4.1.2 Analysis | Table 6-13 ODQ summaries at baseline and week 18<br>Table 6-14 Frequencies of level of improvement for the ODQ scores<br>Table 6-15 Model estimates for ODQ<br>Table 6-16 Summary statistics for ODQ by cross-over status | Included descriptive statistics of baseline and week 18 ODQ score and added histogram split by group.<br>Included descriptive statistics of ODQ scores split by cross-over status and |

| | | |
|---|---|---|
| | Figure 6-1 Distribution of the differences the in baseline and week 18 ODQ scores | treatment actually received at baseline and week 18. |
| 17.4.2 ODQ at 30, 42 and 54 weeks after randomisation / 17.4.2.2 Analysis | Table 6-20 Change from baseline summaries for ODQ<br>Table 6-21 Parameter estimates for ODQ longitudinal model<br>Figure 6-2 Profile plots of ODQ scores | Included mean profile plots alongside change from baseline summaries. |
| 17.4.3 Numerical rating scores for leg pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation / 17.4.3.2 Analysis | Table 6-24 Change from baseline summaries for leg pain rating<br>Table 6-25 Parameter estimates for leg pain rating longitudinal model<br>Table 6-26 Summary statistics for leg pain rating by cross-over status<br>Figure 6-3 Profile plots of leg pain rating | Included mean profile plots alongside change from baseline summaries.<br><br>Included descriptive statistics of leg pain scores split by cross-over status and treatment actually received at week 18. |
| 17.4.4 Numerical rating scores for back pain at baseline, and at 18, 30, 42 and 54 weeks after randomisation / 17.4.4.2 Analysis | Table 6-28 Change from baseline summaries for back pain rating<br>Table 6-29 Parameter estimates for back pain rating longitudinal model<br>Table 6-30 Summary statistics for back pain rating by cross-over status<br>Table 6-28 Change from baseline summaries for back pain rating<br>Figure 6-4 Profile plots of back pain rating | Included mean profile plots alongside change from baseline summaries.<br><br>Included descriptive statistics of back pain scores split by cross-over status and treatment actually received at week 18. |
| 17.4.5 Likert Scale to assess patient treatment satisfaction at 54 weeks after randomisation / 17.4.5.2 Analysis | Table 6-32 Summaries for Likert scale for satisfaction with care at week 54<br>Table 6-33 Mann-Whitney results | Median, IQR and median difference presented (rather than mean, SD and mean difference) for Likert scale as more appropriate for skewed data.<br><br>Included median profile plots alongside week 54 summaries. |
| 17.4.6 Modified Roland-Morris outcome score for sciatica at baseline, and at | Table 6-34 Change from baseline summaries for MRM<br>Table 6-35 Parameter estimates for the MRM longitudinal model | Included mean profile plots alongside change from baseline summaries. |

| | | |
|---|---|---|
| 18, 30, 42 and 54 weeks after randomisation / 17.4.6.2 Analysis | **Error! Reference source not found.**<br>Figure 6-6 Profile plots of modified Roland-Morris scores | |
| 17.4.7 Core Outcome Measures Index (COMI) at baseline, and at 18, 30, 42 and 54 weeks after randomisation / 17.4.7.2 Analysis | Table 6-37 Change from baseline summaries for COMI<br>Table 6-38 Parameter estimates for the COMI longitudinal model<br>Figure 6-7 Profile plots of COMI score | Included mean profile plots alongside change from baseline summaries. |
| 17.4.8 Work status at follow-up / 17.4.8.2 Analysis | Table 6-40 Employment summaries at baseline and follow up<br>Table 6-41 Two way table for Chi-square test of association - week 18<br>Table 6-42 Two way table for Chi-square test of association - week 54 | Summaries for the number of work days lost could not be presented. |
| 18 Missing data and withdrawals | Table 6-17 Model estimates for ODQ with imputed data | |
| 19 Additional analyses / Additional analysis 1 | Table 6-18 Model estimates for the extended primary outcome mixed effects model<br>Table 6-19 Parameter estimates for extended model included disc prolapse level | Included a further post-hoc analysis based on the additional analysis model which also included disc prolapse level. |
| 20 Safety Evaluations / 20.1 Data sets analysed | Table 6-2 Data sets analysed | |
| 20 Safety Evaluations / 20.2 Presentation of the data | Table 6-9 Adverse events overall<br>Table 6-10 Adverse events by severity<br>Table 6-11 Line listings of adverse events by causality | Line listings for the relationship to intervention were presented rather than a table summarising frequencies as there multiple levels of causality for the TFESI. |

**Appendix 2: Other reasons for eligible patients not being approached for consent**

The other reasons provided for eligible patients not being approached for consent are presented below as line listings and the frequencies of these is also presented if similar reasons are grouped together.

| Other Reason |
|---|
| sent postal info/phoned- no response |
| In prison - unable to contact |
| did not attend apt |
| non compliant with treatments |
| patient transferred to private care |
| Patient gone private |
| Symptoms need to be managed conservatively |
| Symptoms resolved. |
| Symptoms had resolved |
| Symptoms resolved |
| Symptoms resolved. |
| Resolution of symptoms |
| Symptoms had improved |
| Improvement in symptoms |
| Improvement in symptoms |
| Improvement in symptoms |
| Improvement in symptoms. |
| Improvement in symptoms. |
| required urgent spinal surgery |
| Already listed and given date for injection |
| already had TFESI |

| Other reason (grouped) | Frequency |
|---|---|
| Already listed and given date for injection | 1 |
| In prison - unable to contact | 1 |
| Patients in private care | 2 |
| Patients symptoms improved/ resolved | 11 |
| Symptoms need to be managed conservatively | 1 |
| already had TFESI | 1 |
| did not attend appt | 1 |
| non compliant with treatments | 1 |
| required urgent spinal surgery | 1 |
| sent postal info/phoned- no response | 1 |

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