

**Assessing Cervical Foraminal Stenosis: Volumetric MRI study in Patients with Cervical Brachialgia**

Version: 5.0

Date: 11/07/2020

Sponsor: Leeds Teaching Hospitals NHS Trust

Sponsor Number: Insert

REC Ref: Insert

IRAS Ref: 285222

Chief Investigator **Mr Simon Thomson**

**Consultant Neurosurgeon**

**Leeds Teaching Hospitals NHS Trust**

**Jubilee Wing, Leeds General Infirmary**

**1 Great George Street**

**Leeds, LS1 3EX**

**E-mail:** [**simon.thomson1@nhs.net**](mailto:simon.thomson1@nhs.net)

**Tel: 0113 3928567**

# Key Contacts

## Chief Investigator

Mr. Simon Thomson

Consultant Neurosurgeon & Honorary Clinical Associate Professor

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Tel: 0151 529 6210

E-mail: [simon.thomson1@nhs.net](mailto:simon.thomson1@nhs.net)

Tel: 0113 3923250

## Co-investigators

Dr. James Meacock

Research Fellow

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email : [James.Meacock@nhs.net](mailto:James.Meacock@nhs.net)

Dr. Stuart Currie

Consultant Neuroradiologist

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email : [stuartcurrie@nhs.net](mailto:stuartcurrie@nhs.net)

Professor David Jayne

Professor of Surgery & Honorary Consultant Surgeon

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email: [D.G.Jayne@leeds.ac.uk](mailto:D.G.Jayne@leeds.ac.uk)

Professor Deborah Stocken

Prof of Research and Director of surgical interventions, diagnostics and devices at Clinical Trials Research Unit (CTRU)

Leeds Institute of Clinical Trials Research Unit

University of Leeds

Woodhouse

Leeds LS2 9JT

Email : [D.D.Stocken@leeds.ac.uk](mailto:D.D.Stocken@leeds.ac.uk)

Tel : 0113 343 5616

Mr. Senthil Selvanathan

Consultant Neurosurgeon

Department of Neurosurgery

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email : [senthil.selvanathan@nhs.net](mailto:senthil.selvanathan@nhs.net)

Dr. Joanna Leng

Senior Research Fellow

Leeds school of computing

University of Leeds

Woodhouse

Leeds LS2 9JT

Email : [J.Leng@leeds.ac.uk](mailto:J.Leng@leeds.ac.uk)

Dr Mark Igra

Consultant Neuroradiologist

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email : [Mark.Igra@nhs.net](mailto:Mark.Igra@nhs.net)

Dr David Broadbent

Medical Physicist

Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds LS9 7TF

Email: [D.Broadbent@nhs.net](mailto:D.Broadbent@nhs.net)

# Table of Contents

1 Key Contacts 2

1.1 Chief Investigator 2

1.2 Co-investigators 2

2 Table of Contents 4

3 Synopsis 7

4 Flow diagram 9

5 Glossary of Terms 10

6 Background 11

7 Lay Summary 13

8 Aims and Objectives 14

8.1 Primary Objective 14

8.2 Secondary Objectives 14

8.3 Exploratory Objectives 14

8.4 Study Null Hypothesis 14

9 Study design 15

9.1 Summary 15

9.2 Number of Participants 15

10 Eligibility 16

10.1 Participant eligibility 16

10.2 Inclusion Criteria 16

10.3 Exclusion Criteria 16

10.4 Concurrent Clinical Studies 16

11 Recruitment 17

11.1 Recruitment setting 17

11.2 Eligibility screening 17

11.3 Informed consent 17

11.4 Loss of capacity 18

11.5 Potential for benefit to research participants 18

11.6 Potential for risk to research participants 18

12 Data Collection 19

12.1 Participant information collected at registration 19

12.2 Data collection at other trial points 19

13 Intervention details 20

13.1 MR scan 20

13.2 Post-acquisition processing of MRI data 20

13.3 Image interpretation 20

13.4 Grading criteria 20

13.5 Computational mathematical modelling 22

13.6 Communication of scan results 22

14 Withdrawal 23

15 Site File and Data Collection 24

15.1 Schedule for data collection 24

15.2 Pregnancy 24

15.3 Death 25

15.4 Definition of end of study 25

16 Safety reporting 26

16.1 General definitions 26

16.2 Reporting of adverse events 26

16.2.1 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) – expedited reporting 27

16.2.2 All other adverse events – Non-expedited reporting 27

16.2.3 Untoward medical events unrelated to the study – Not reportable 27

16.3 Responsibilities for adverse event reporting 28

16.4 Onward reporting 28

17 Outcome measures 29

17.1 Primary outcome measure 29

17.2 Secondary outcome measures 29

18 Statistical Considerations 31

18.1 Sample size 31

18.2 Planned recruitment rate 31

18.3 Statistical analysis 31

18.3.1 Missing data 32

19 Study Monitoring 33

20 Quality Assurance and Ethical Considerations 34

20.1 Trial administration and logistics 34

20.2 Serious Breaches 34

20.3 Ethical Approval 34

21 Confidentiality 35

21.1 MRI data 35

21.2 Archiving 35

22 Statement of Indemnity 36

23 Study organisational structure 37

23.1 Operational structure and responsibilities 37

23.2 Financing 37

24 Publication policy 38

25 References 39

# Synopsis

|  |  |
| --- | --- |
| Title | Assessing Cervical Foraminal Stenosis: Volumetric MRI study in patients with cervical nerve root compression |
| Design | This is a non-randomised single institution study to develop a novel imaging technique of the cervical nerve root canal.  Patients will be recruited pre-operatively from surgical waiting lists at the Leeds Teaching Hospital NHS Trust. An additional three-dimensional volumetric MRI scan of the cervical spine will be obtained.  The anatomy of the cervical nerve root canal will be analysed. We will measure the degree of nerve root compression and analyse which imaging features of root compression best predict surgical outcome. We will also be exploring if we can use automated computational mathematical modelling to measure root compression. |
| Aim | **Primary Objective:**  To assess whether the maximum degree of root canal stenosis when measured on modified plane imaging is better at predicting the improvement in neck disability index 6 weeks post-operatively than when measured on standard axial MRI scans  **Secondary Objectives**:  To assess whether the length or location of root canal stenosis when measured on modified plane imaging is better at predicting surgical outcome (neck disability, arm pain, motor and sensory loss) than when measured on standard axial MRI scans  To assess whether the maximum degree of root canal stenosis, location of stenosis or length of stenosis when measured on modified plane imaging is better at predicting pre-operative clinical symptoms including arm pain, sensory loss and myotome weakness than when measured on standard axial MRI scans  To assess whether inter and intra-rater correlation of stenosis, length and location of compression is improved by modified plane imaging over standard axial MRI scans  **Exploratory Objectives:**  To use mathematical modelling techniques to automate the measurement of nerve root canal stenosis  To develop a scoring system that reflects the type, location, length and severity of root canal stenosis and that correlates with symptom severity and surgical outcome. |
| Population: | Patients with symptomatic cervical brachialgia with at least six weeks of symptoms who are awaiting surgical intervention. |
| Number of Participants: | n=20 |
| Inclusion Criteria | 1. Age over 18 years 2. Diagnosis of brachialgia 3. Able to provide fully informed written consent 4. Able to lie flat for 1 hour in an MRI scanner 5. Awaiting either an anterior cervical discectomy or a posterior cervical foraminotomy for brachialgia 6. Females of childbearing age must be using effective contraception 7. Sufficient understanding of English to participate in the trial |
| Exclusion Criteria | 1. Cervical myelopathy 2. Radiological evidence of cord compression 3. History of cervical trauma 4. Evidence of suspected or histologically proven tumour 5. Previous cervical spine surgery 6. Non-MRI compatible implantable device e.g. pacemaker 7. Unable to have MRI scan due to claustrophobia 8. Female participants must not be pregnant and if of childbearing age must be using adequate contraception |
| Interventions: | A single MRI scan will be performed for each participant |
| Study Duration: | The study will be conducted between August 2020 and July 2021 |

# Flow diagram

# Glossary of Terms

|  |  |
| --- | --- |
| **Abbreviation** | **Full expansion** |
| ACD | Anterior Cervical Discectomy |
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASIA | American Spinal Injury Association |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CSF | Cerebrospinal Fluid |
| CT | Computerised Tomography |
| GP | General Practitioner |
| Inter-observer reliability | Consistency between two different observers |
| Intra-observer reliability | Consistency between two separate observations of the same data by a single observer at two different points in time |
| MDI | Myelopathy Disability Index |
| MRI | Magnetic Resonance Imaging |
| NDI | Neck Disability Index |
| NHS | National Health Service |
| PCF | Posterior Cervical Foraminotomy |
| PI | Principle Investigator |
| R&D | Research and Development |
| SPSS | Statistical package for the social sciences |
| T | Tesla |
| VAS | Visual Analogue Scale |
| XR | X-Ray |

# Background

The natural process of aging leads to degenerative changes within the spine including disc prolapse, osteophyte formation, facet joint hypertrophy and ligamental thickening. All these may lead to stenosis (narrowing) of a nerve root foramen (canal) through which the neck (cervical) nerve passes. Thus, cervical foraminal stenosis is a common consequence of ageing leading to compression and pain radiating down the arm (Rao, 2002). Nerve root compression is called radiculopathy, the symptom of radiating arm pain is known as brachialgia and the syndrome may lead to significant disability in the patients that are affected. The mean age of patients affected is 49, although it may occur at any age, patients most commonly present over the age of 40 (Alvin et al., 2016; Tumialán et al., 2010). If severe, root compression may lead to loss of function in the upper limb. In the >110,000 cases of brachialgia that occur in the UK each year, around 75% resolve over several months with non-surgical management (Caridi et al., 2011) but those that do not resolve will frequently require surgical intervention. This condition therefore represents a significant and growing burden on the National Health Service (Carette, 2005).

The main surgical treatment options for brachialgia include: Anterior Cervical Discectomy (ACD); Posterior Cervical Foraminotomy (PCF); Anterior Cervical Disc Replacement; and Anterior Cervical Foraminotomy. Of these, ACD and PCF are performed most frequently. Owing to its anterior cervical approach, ACD comes with significant, potentially irreversible, risks of dysphagia and hoarse voice (Fountas et al., 2007). PCF avoids the risks associated with an anterior approach but has been shown to be associated with a higher incidence of post-operative neck pain (Wang et al., 2015). Presently, there is no clinical guidance based on high quality research to support which patients should undergo which surgical procedure. Specifically, it is unknown whether one operation works better than the other for certain types, lengths or locations of nerve root compression (Yousem et al., 1991). Currently the decision on surgical procedure type is typically made based on a surgeon’s experience and preference.

This decision to perform one or other operation is often guided by the findings on pre-operative magnetic resonance imaging (MRI) of the cervical spine. However, despite MRI providing excellent non-invasive imaging of the spine its use as a tool to assess foraminal stenosis could be improved. The site and length of nerve root compression varies from patient to patient and visualisation of the compressed nerve root will be affected by the MRI protocol including the imaging sequence and the plane used (Lee et al., 2017). Cervical root canal stenosis is usually reported using subjective terms such as “minor”, “moderate” and “severe”. We believe that there is scope to improve the MRI technique so that it can be used to better assess the location and degree of nerve root compression. Improved radiological assessment may provide a more standardised approach for patients to be stratified into a surgical procedure. Whilst rarely utilised, there are several published techniques that can be used to grade the degree of cervical foraminal stenosis.

Bartlett et al. (1998) reviewed 20 patients using standard T2-weighted MRI scans of the cervical spine. 3 grades were created, Grade 0 was the absence of foraminal stenosis, Grade 1 was osteophyte or disc contact with the nerve root and Grade 2 was >50% narrowing of the foramen. This study was an early attempt to develop a scoring system. It was suggested that further research into Grade 2 compression was necessary to better refine how foraminal stenosis was related to nearby structures and their dimensions. There was no attempt to measure the length of the compression, to define whether the compression was anterior or posterior or to correlate the imaging findings with symptoms or surgical outcome.

Kim et al. (2015) reviewed 96 patients using standard T2-weighted axial MRIs of the cervical spine. 3 grades were created, Grade 0 was the absence of foraminal stenosis, Grade 1 indicated that the narrowest width of the neural foramen was >50% of the width of the extra foraminal nerve root, Grade 2 indicated that the width of the neural foramen was ≤50% of the width of the extra foraminal nerve root. This grading criteria built upon previous methods by relating stenosis to the extra foraminal nerve root but, as with the Bartlett et al. grading, this scoring system lacks an assessment of the length or location of the compression and does not offer correlation of the radiological findings with symptoms or surgical outcome.

Park et al. (2013) reviewed 50 patients using T2-weighted oblique sagittal MRIs of the cervical spine. In this study 4 grades were created, Grade 0 was the absence of foraminal stenosis, Grade 1 was mild (<50% of root circumference), Grade 2 was moderate (>50% of root circumference) and Grade 3 was severe foraminal stenosis (nerve root collapse). This study utilised non-standard oblique MRI views that are not available in routine clinical practice, the length and location of the compression was not graded and there was no attempt to correlate findings with symptoms and surgical outcome.

Park et al. (2014) reviewed 166 patients using the Park system described above and showed 99% specificity but only 39% sensitivity for the presence of clinical symptoms.

Park et al. (2015) reviewed 356 patients using standard T2-weighted axial MRIs of the cervical spine. They used the system outlined by Kim and a modification on this system to attempt to correlate this with clinical outcomes. The authors could not adequately correlate the radiological score with clinical symptoms.

Lee et al (2017) compared the Park, Kim and modified Kim systems in their ability to correlate with clinical symptoms. The Park and Modified Kim systems had high correlation coefficients whereas the unmodified Kim system had moderate correlation only.

A comprehensive systematic review has been undertaken in our institution that shows that improvements can be made both to the MRI technique and to the scoring system used so that it better correlates with clinical symptoms and more accurately predicts the response to surgery. We have applied the described scoring systems to surgical patient imaging to assess the inter- and intra-rater consistency and we are conducting a study on healthy volunteers to develop a better way to image the nerve root canals.

In this study we will be comparing the standard techniques described above with the modified plane MRI technique and comparing how it correlates with symptoms and predicts surgical outcome. We are also exploring whether mathematical modelling techniques can be used to automate the process of measuring cervical nerve root canal stenosis.

# Lay Summary

Currently standard MRI scans for trapped nerves in the neck are performed using sequential horizontal and vertical cuts through the spine separated by 2 or 3 millimetres. However, the nerves travel in a canal that is neither in the horizontal or vertical plane and the nerve itself is 2 to 3 mm in diameter. Consequently, nerve root compression can be rather poorly demonstrated on standard MRI sequences. Furthermore, the currently published scoring systems are not well validated and are therefore rarely used in clinical practice.

We will be using standard MRI techniques but at a different angle to image the nerves in the neck at high resolution as they leave the spine. The scans will be angled so that they cut exactly along and across the nerve canal. We are interested to see how this imaging matches the symptoms and whether different locations of compression better respond to one of the two main operations that can be performed.

Patients who are awaiting surgery to treat cervical brachialgia, will be recruited from pre-operative surgical waiting lists. They will be invited to participate in the trial. If they agree to participate, we will record some information (see section 12 for more detail) and perform an additional pre-operative MRI scan. Post-operatively we will assess symptoms 1 day and 6 weeks after the operation.

We will measure the width of the nerve canal on standard images and on the images angled along and across the nerve to see which technique is best at predicting the symptoms of nerve root compression and the response to surgical decompression.

# Aims and Objectives

## Primary Objective

To assess whether the maximum degree of root canal stenosis when measured on modified plane imaging is better at predicting surgical outcome than when measured on standard axial MRI scans

## Secondary Objectives

To assess whether the length or location of root canal stenosis when measured on modified plane imaging is better at predicting surgical outcome (neck disability, arm pain, motor and sensory loss) than when measured on standard axial MRI scans

To assess whether the maximum degree of root canal stenosis, location of stenosis or length of stenosis when measured on modified plane imaging is better at predicting clinical symptoms including arm pain, sensory loss and myotome weakness than when measured on standard axial MRI scans

To assess whether inter and intra-rater correlation of stenosis, length and location of compression is improved by modified plane imaging over standard axial MRI scans

## Exploratory Objectives

To use mathematical modelling techniques to automate the measurement of nerve root canal stenosis

To develop a scoring system that reflects the type, location, length and severity of root canal stenosis and that correlates with symptom severity and surgical outcome.

## Study Null Hypothesis

There is no difference in the ability of standard imaging and modified plane imaging to predict surgical outcome.

# Study design

## Summary

This is a non-randomised single institution study to explore whether modified plane MR imaging of the cervical nerve root canal can be used to predict surgical outcome

Pre-operative patients will be recruited from surgical waiting lists with symptomatic cervical brachialgia for at least six weeks.

An additional three-dimensional volumetric MRI scan of the cervical spine will be performed. The data from this will be used to build “standard” T2 axial views with a 2mm slice thickness. The data will also be used to build modified plane images that align with and are at cross section to the nerve root.

Clinical data including the presence of arm pain, neck pain, arm sensory or motor changes will be assessed. The neck disability score will be used as a functional score. Baseline assessments will be made on the day of surgery, one day and six weeks after the operation.

The anatomy of the cervical nerve root canal will be analysed to measure the degree of maximal nerve root compression and the length and position of this compression. We will compare the ability of standard and modified plane images to predict clinical symptoms and surgical outcome. Inter and intra rater consistency will also be measured for each type of scan.

Automated mathematical modelling measurements of the root canals will also be made, and the consistency of these measurements calculated.

## Number of Participants

There will be a total of 20 participants.

# Eligibility

## Participant eligibility

Eligibility waivers to inclusion or exclusion criteria are not permitted.

## Inclusion Criteria

Participants will be eligible for the study if they fulfil the following inclusion criteria:

1. Age over 18 years
2. Diagnosis of brachialgia
3. Able to provide fully informed written consent
4. Able to lie flat for 1 hour in an MRI scanner
5. Awaiting either an anterior cervical discectomy or a posterior cervical foraminotomy for brachialgia
6. Females of childbearing age must be using effective contraception
7. Sufficient understanding of English to participate in the trial

## Exclusion Criteria

Participants will be ineligible for the study if they fulfil the following exclusion criteria:

1. Cervical myelopathy
2. Radiological evidence of cord compression
3. History of cervical trauma
4. Evidence of suspected or histologically proven tumour
5. Previous cervical spine surgery
6. Non-MRI compatible implantable device e.g. pacemaker
7. Unable to have MRI scan due to Claustrophobia
8. Female participants must not be pregnant and if of childbearing age must be using adequate contraception

## Concurrent Clinical Studies

Where recruitment into another study is considered to be appropriate and unlikely to have any detrimental effect on this study then recruitment will be permitted but must first be discussed with the Chief Investigator.

# Recruitment

## Recruitment setting

Participants will be recruited from the neurosurgical centre at Leeds Teaching Hospital NHS Trust to participate in the study. No remuneration will be offered. There will be a total of 20 participants over the duration of the trial.

## Eligibility screening

Participants will be screened against the inclusion and exclusion criteria to assess eligibility

## Informed consent

Participants will provide written informed consent.

Following information provision, participants must be given the opportunity to discuss the study with their family and healthcare professionals before they are asked whether they would be willing to take part in the study. Participants will be given as much time as possible to consider their participation in the study; ideally, they will be allowed 24 hours as a minimum. The right of a patient to refuse consent without giving reasons will be respected.

Informed consent may only be obtained by the Chief Investigator (CI) or an appropriate, delegated, healthcare professional. The Chief Investigator (CI) retains overall responsibility for the informed consent of participants and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

A record of the consent process detailing the date of consent and all those present will be detailed in the site file. The original consent form will be filed in the study site file, a copy of the consent form will be given to the participant. Where a participant is required to re-consent or new information needs to be provided to a participant, it is the responsibility of the CI to ensure this is done in a timely manner.

The participant will be free to withdraw from the study at any time without giving reasons and without prejudicing any treatment/care.

The participants GP and responsible clinician will be informed when a participant is recruited.

## Loss of capacity

Loss of mental capacity of a participant after giving informed consent for the study is expected to be a rare occurrence. Should this eventuality occur no further study procedures or data collection will occur from this point. Any data collected up to the point of withdrawal will be kept on record and used in the analysis.

## Potential for benefit to research participants

The research participants will have the chance to see the scans of their cervical spine. Their participation will help future patients and doctors to treat this condition.

## Potential for risk to research participants

There are no investigational risks to the participants expected through the use of a clinical 3T MRI machine. All images will be reviewed by a neuroradiologist to exclude unexpected findings. Should an unexpected finding be discovered the patient’s GP will be informed and the appropriate clinical referral will be made.

# Data Collection

## Participant information collected at registration

Information collected at registration will include the following:

* Age, date of birth and initials
* Clinical history of cervical spine disease
* Smoking status
* GP details
* Inclusion and Exclusion criteria

## Data collection at other trial points

Information collected prior to the MRI, pre-operatively, day 1 and week 6 following surgery will include:

* Modified ASIA score
* Neck Disability Index (NDI)
* Numbered rating scale (NRS) pain score for neck and arm pain
* PainDETECT questionnaire

# Intervention details

## MR scan

The scans will be acquired using a 3T MRI scanner which is situated in the Advanced Imaging Centre at the Leeds General Infirmary. The standard pre-MRI safety screening questionnaire will be used.

High definition, 3-dimensional cervical spine T2 datasets will be acquired. Diffusion weighted sequences will also be obtained.

The scans will cover both sides and the cervical nerve root levels from C2/3 to C7/T1 inclusive.

## Post-acquisition processing of MRI data

Following acquisition, the 3d datasets will be processed to generate:

* Standard axial T2 weighted cross sectional images
* 2 dimensional T2 images aligned along the nerve root
* 2 dimensional oblique T2 images in cross section to the nerve root
* 2 dimensional diffusion weighted images

## Image interpretation

Six observers will independently review the images blinded to the demographics and background of the participant. The grading systems will be given to the observers with a detailed written description and diagrammatic representation of how to interpret the images presented to them. The observers will then rate the degree of cervical foraminal stenosis bilaterally against the set criteria.

To determine the intra-rater variability the same observer will be given the same images, following a wash out period of one month to reduce bias.

## Grading criteria

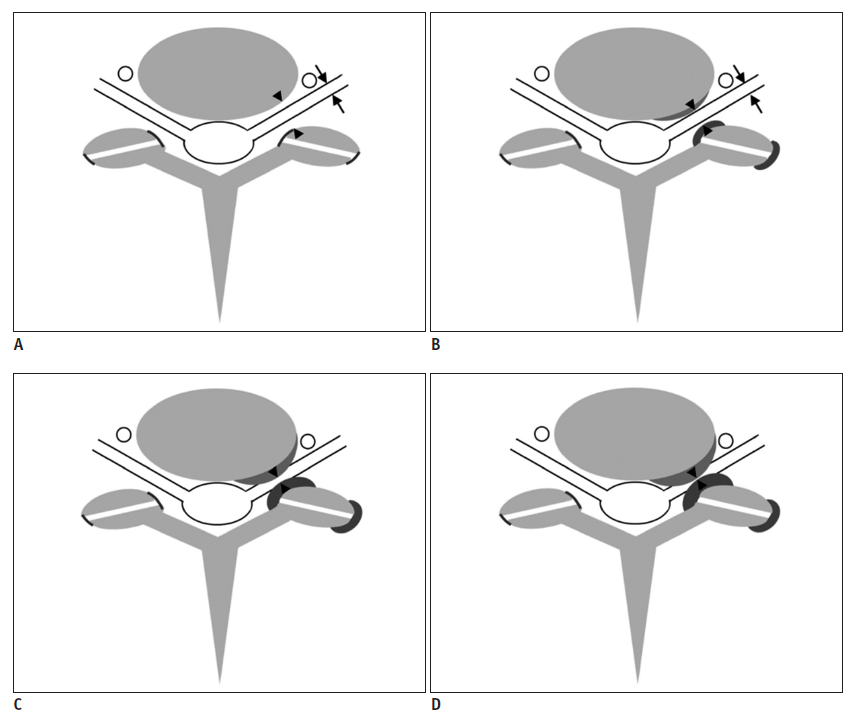
**Subjective score (all views)**

a) Mild

b) Moderate

c) Severe

**Figure 1: Schematic for measurements of the nerve root canal on axial imaging**



**Kim and modified Kim (axial slices only)**

a) Measurement of uncompressed nerve root diameter once exited the foramen (Blue)

b) Measurement of maximal compressed nerve root diameter within foramen (Orange)

c) Ratio of Item a: Item b

**Park system (oblique sagittal T2 views)**

1. Measurement of perineural fat obliteration compared to nerve root circumference
2. Presence / Absence of morphological change or collapse of the nerve root

**Anterior v posterior compression (all views)**

a) Measurement of anterior compression from bony margin (Green)

b) Measurement of posterior compression from bony margin (Green)

c) Type of compression is it disc, osteophyte, both or unknown. Based on T2 signal.

**Laterality of compression (all views)**

a) Measurement of the point of maximum compression. This is a measurement from the apex of the ligamentum flavum to the maximum compression (Red)

b) Is the point of maximal compression:

i. Medial to the root canal

ii. Proximal 50% of the nerve root canal

iii. Distal 50% of the nerve root canal

**Length of compression (all views)**

Length of neuroforamina diameter that is less than uncompressed nerve root diameter (Yellow) or 2.6mm if nerve diameter is unrecordable.

## Computational mathematical modelling

The MRI data will be imported into graphics software so that it can be interactively manipulated and viewed to improve the ability of the medical experts to assess the volunteers’ condition. From this we will be able to create a general model of the condition that will be used as the basis of semi-automated visualisation and assessment tools.

## Communication of scan results

All scans will be reported by a Consultant Neuroradiologist. The results of the scans will be communicated to the participant’s GP.

# Withdrawal

Participants will not be withdrawn from the study unless it is harmful for the participant to continue or unless the participant wishes to be withdrawn. In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

In the event that a participant withdraws prior to imaging, the non-participation log should be completed. An additional patient may be recruited to replace the patient who has declined to continue. No further data will be collected for this participant, but any data already collected can be used as part of the study.

If a participant withdraws during the MRI scan, we will seek a replacement to ensure that the project includes 20 complete MRI datasets.

# Site File and Data Collection

The research team will maintain a file of essential study documentation and keep copies of all completed CRFs for the study. The CRFs will contain the participant’s unique study number, date of birth, and initials. Clinical data will only be collected following recruitment and consent.

## Schedule for data collection

The data collected is summarised in table 1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Events | Eligibility and Registration | MR safety screen | Modified ASIA | NDI | Pain Detect | NRS neck & arm pain |
| Consent and Registration | √ |  |  |  |  |  |
| Pre-MR assessment |  |  | √ | √ | √ | √ |
| MRI scan |  | √ |  |  |  | √ |
| Pre-op assessment |  |  | √ | √ | √ | √ |
| 1 day post-op |  |  | √ | √ | √ | √ |
| 6 weeks post-op |  |  | √ | √ | √ | √ |
| Safety events | √ | √ | √ | √ | √ | √ |

**Table 1: Schedule of Events**

## Pregnancy

Any suspected or confirmed pregnancies between the date of recruitment to the date of the MRI scan will be recorded. All further protocolised treatment must be stopped immediately if a pregnancy occurs or is suspected during this time.

## Death

All deaths occurring between registration and the MRI scan must be recorded. Data collected will include but not be limited to:

* + Date of death
  + Cause of death

## Definition of end of study

The end of the study is defined as the date of the last participant’s last data item corresponding to the date of the MRI scan.

# Safety reporting

## General definitions

An adverse event (AE) is defined as an untoward medical event in a participant, which has a causal relationship to the study. The study includes the study intervention and any further treatment related to the study intervention (such as treatment of complications caused by the intervention and any study-specific interventions e.g. the consent process and completion of questionnaires).

An untoward medical event can include:

* + any unintentional, unfavourable clinical sign or symptom
  + any new illness or disease or the deterioration of existing condition
  + any clinically relevant deterioration in any clinical tests

A serious adverse event (SAE) is defined as a complication which:

* + results in death
  + is life-threatening
  + requires in-patient hospitalisation or prolongation of existing hospitalisation
  + results in persistent or significant disability or incapacity
  + consists of a congenital anomaly or birth defect, or
  + is otherwise considered medically significant by the investigator

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious complication which is related and unexpected and will require expedited reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms related and unexpected as:

* + Related: that is, it resulted from administration of any research procedures. All complications by definition are related to the study procedures.
  + Unexpected: that is, the type of event that in the opinion of the investigator is not considered expected.

Medical and scientific judgement must be exercised in deciding whether an event is serious. These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

## Reporting of adverse events

Information on all complications will be collected for this study whether volunteered by the participant, discovered by investigator questioning or detected through physical examination or other investigation.

## Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) – expedited reporting

All Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring within 6 weeks of the study are subject to expedited reporting requirements and must therefore be notified to the sponsor within 24 hours of the clinical research staff becoming aware of the event.

For each SAE and SUSAR, the following data will be collected:

* + Start and end dates of event, if resolved
  + Full details of complication in medical terms with a diagnosis (if possible)
  + Action/intervention
  + Outcome
  + An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site)

## All other adverse events – Non-expedited reporting

Information about the incidence and severity of all other adverse events (this includes all non-serious expected and unexpected events) which occur from the date of recruitment until 6 weeks post completion will be collected for all participants. These events will not be subject to expedited reporting requirements.

## Untoward medical events unrelated to the study – Not reportable

It is anticipated that there will be minimal additional risks associated with the intervention in this study. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to the study procedures.

## Responsibilities for adverse event reporting

Chief Investigator (CI)

Checking for adverse events during admission and follow-up, including judgment in assigning:

* + Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
  + Seriousness
  + Expectedness
  + To ensure all SAEs and SUSARs up to 6 weeks post-surgery are recorded and reported to the sponsor within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.
  + To report SAEs and SUSARs in-line with the protocol.
  + To report SAEs and SUSARs to local committees in line with local arrangements.
  + Undertake review of SAEs and SUSARs

## Onward reporting

Safety issues will be reported to the REC as part of the annual progress report.

An annual summary of complications will be reported to the Sponsor.

Expedited reporting of events to the REC and Sponsor will be subject to current guidance and Sponsor requirements.

# Outcome measures

## Primary outcome measure

Neck disability index at 6 weeks is used as the primary outcome measure.

The NDI is the most widely used and well validated instrument for assessing self-rated disability in patients with neck pain and brachialgia. It has been reported in over 300 publications in both clinical and research settings for quantifying this common problem. NDI is a core instrument for measuring the degree of disability or dependence in the daily activities of patients with brachialgia and has been recommended as a well-suited outcome measure for designing trials in this patient population (Rodine and Vernon, 2012).

The NDI is a 10-item, 50-point index that assesses different aspects of daily functioning in patients with neck pain. It comprises four items regarding subjective symptoms (pain intensity, headache, concentration, sleeping), four items regarding activities of daily living (lifting, work, driving, recreation), and two items regarding discretionary activities of daily living (personal care, reading) (Wainner et al., 2003). Each item is scored from 0 (best) to 5 (worst) and the total score is expressed either as a raw score (0-50) or as a percentage (% score), with a higher score corresponding to greater disability. The primary endpoint will be expressed as a percentage score. It has been shown to be a valid and reliable outcome measure in brachialgia (Cleland et al., 2006; Young et al., 2009, 2010).

NDI exhibits excellent test-retest reliability in patients with cervical radiculopathy and has been found to demonstrate adequate responsiveness in this patient population (Young et al., 2010). Several large studies including randomised trials studying brachialgia have used NDI to measure outcome (Garrido et al., 2010; Lawton et al., 2014; Nunley et al., 2009; Skovrlj et al., 2014).

Various studies have been conducted to determine the minimally important clinical difference on NDI (Cleland et al., 2008; Riddle and Stratford, 1998; Westaway et al., 1998; Young et al., 2009). A study by Stratford et al 1999 which has the highest reliability reported a change of 5 out of 50 points (corresponding to 10%) is the minimally clinically important difference (Stratford, 1999; Young et al., 2010).

## Secondary outcome measures

Neck Disability Index (NDI) 1 day post-surgery

Numerical Rating Scales for neck and upper limb pain 1 day and 6 weeks post-surgery.

The pain NRS is a unidimensional 11 step measure of pain intensity, including pain in the cervical and arm areas. It has been shown to correlate well with the more commonly used visual analogue scales, but tended to promote better compliance and was easier to use for participants (Hjermstad et al., 2011). It comprises a horizontal line marked from 0 to 10 in equidistant intervals with one end denoting “no pain” (score of 0) and the other “worst imaginable pain” (score of 10). It is self-completed by the respondent who is asked to mark the number on the scale that represents their pain intensity. The score is the number marked by the participant.

PainDETECT (Freynhagen et al., 2006)

A questionnaire aimed at assessing whether the pain experienced by a patient is neuropathic in nature. It will be collected at day 0 and at 1 day and 6 weeks post-surgery. It consists of a total of 12 items, including three numerical rating scales that range from 0 to 10 to measure pain intensity, seven descriptive scales where the respondent can choose from six possible descriptions that describe the type of pain, and 2 items aimed at graphically describing the location and course of the respondent’s pain.

The overall score ranges from 0 to 38, with a score of 0 to 12 inclusive indicating that neuropathic pain is unlikely (<15%), and scores between 19 and 38 inclusive indicating that neuropathic pain is likely (>90%). Scores of 13-18 are ambiguous. Overall score is calculated by summing the numerical scores corresponding to each descriptor for the seven descriptive scales, and modifying it based on the responses given for the two graphical items. It is important to note that scores from the numerical rating scales do not contribute to the overall score but will be reported as separate items. It is also important to note that burning pain will be analysed separately as this is a feature of neuropathic pain but does not respond well to surgical decompression.

Modified ASIA score

Extent and severity of spinal cord and upper limb functional impairment using a restricted version of the ASIA score at the pre-operative assessment, and at 1 day and 6 weeks post-surgery

ASIA is a system of tests, developed by the American Spinal Injury Association, used to define and describe the extent and severity of a patient’s functional impairment as a result of nerve entrapment or other spinal injury (Singh, 2017). The patient’s score is based on how much sensation he or she can feel at multiple points on the body, as well as tests of motor function, as assessed by the examiner.

In this trial, it is considered excessive to assess all sensory areas, and so sensory assessment is restricted to the following regions: C4, C5, C6, C7, C8, T1, T10, L2, L4 and S1. The sensory assessment is performed twice for each area, once using light-touch sensation and once using pin-prick sensation. Each test is scored from 0 (sensation is absent) – 2 (sensation is normal), and so the highest possible score for the sensory examination is 40 for each of the two sensations, giving a maximum of 80 overall. Motor function is assessed across 20 different muscles, each scored from 0 (total paralysis) - 5 (Active movement, full range of motion, against gravity and provides normal resistance). The maximum possible score for this component is 100. A lower score is indicative of a greater degree of functional impairment.

Incidence of surgical complications up to 6 weeks post-surgery:

Complications occurring during the initial trial operative procedure and post-operative complications up to 6 weeks post-surgery will be recorded.

# Statistical Considerations

## Sample size

A total of 20 subjects are required. This study will build on an earlier pilot of healthy volunteers on how to best image the cervical nerve root canals. The data obtained from this study will be used to perform sample size calculations for a possible future randomised control trial that will be powered to show significance.

## Planned recruitment rate

Study participants will be recruited and screened over a six month period.

## Statistical analysis

The volumetric MRI scans will be obtained and analysed using the published grading criteria. There will be 3 main analyses carried out (Kang et al., 2011; Kundel and Polansky, 2003) to evaluate the intra-observer and inter-observer reliability of the grading systems:

* Percentage agreement
* Kappa statistics
  + - Poor (κ < 0.1)
    - Slight (0.1 ≤ κ ≤ 0.2)
    - Fair (0.2 < κ ≤ 0.4)
    - Moderate (0.4 < κ ≤ 0.6)
    - Substantial (0.6 < κ ≤ 0.8)
    - Nearly perfect (0.8 < κ ≤ 1.0)
* Intraclass correlation coefficient (ICC)
  + - Poor (<0.4)
    - Good (0.4 – 0.75)
    - Excellent (>0.75)

Nonparametric Spearman correlation analysis will be used to calculate the correlation coefficients (R) between reader grade and clinical manifestations (Cohen, 1988). p values of less than 0.05 will be considered statistically significant. These will be as follows:

* Very high correlation (r value > 0.9)
* Relatively high correlation (r value 0.7 - 0.9)
* Moderate correlation (r value 0.3 - 0.7)
* Weak correlation (r value 0.1 - 0.3)

The statistical package for the social sciences (SPSS) for windows will be used for statistical analysis.

## Missing data

The amount of missing data and reasons why data is missing will be assessed but we do not expect to have much missing data. Data will be chased until received and where this is not possible it will be documented.

# Study Monitoring

The study will be supervised by the sponsor in accordance with the principles of GCP and in-line with the NHS Research Governance Framework (RGF).

# Quality Assurance and Ethical Considerations

## Trial administration and logistics

This trial will adhere to the European Directive on clinical trials 2001/20/EC. It will be conducted in compliance with the protocol, MRC guidelines for GCP in Clinical Trials (1998), the Data Protection Act (DPA G0027154), the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, Ionising Radiation (Medical Exposure) Regulations 2000, MHRA Good Clinical Practice Guidance and other regulatory requirements, as appropriate. The Leeds Teaching Hospitals NHS Trust is the sponsor of this study in accordance with the principles of Good Clinical Practice (GCP).

## Serious Breaches

The study is being conducted in accordance with the professional and regulatory standards for non-commercial research in the NHS under Research Governance Framework for Health and Social Care. The Sponsor has systems in place to ensure that serious breaches of GCP or the study protocol are picked up and reported.

## Ethical Approval

The research is undertaken utilising the pre-existing ethical approval for healthy volunteer research on the advanced imaging centre scanner. Reference number.

# Confidentiality

All information collected during the course of the study will be kept strictly confidential. Information will be held securely whether on paper or electronic and the study will comply with all aspects of the general data protection regulations. Operationally this will include:

* + Explicit written consent from participants to record personal details including name, date of birth and NHS number.
  + Appropriate storage, restricted access and disposal arrangements for participants’ personal and clinical details.
  + Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.
  + Consent from participants for the data collected for the study to be used to evaluate safety and develop new research.
  + Copies of participant’s consent forms, which will include participant’s names, will be collected when a participant is recruited into the study.

If a participant withdraws consent from further participation and/or further collection of data, their data will remain on file and will be included in the final study analysis.

## MRI data

Imaging data will be anonymised at source with a unique identification number. This will be transferred electronically via a secure network within the NHS firewall and will be stored on a secure NHS server, which will require individual password access.

Imaging analysis will be performed on anonymised data using the specialised software on specific computers within the secure network by trial team members. The details of the participants involved will be stored in a database which will be password protected on an NHS computer. No information will be stored on personal computers or laptops. Paper records (consent and clinical record forms) will be stored in a locked cabinet within a locked office.

## Archiving

At the end of the study, all data will be securely archived in line with the Sponsor’s procedures for a minimum of 15 years.

# Statement of Indemnity

Clinical negligence indemnification for UK sites will rest with the participating NHS Trust or Trusts under standard NHS arrangements. Standard NHS indemnity will apply to this study.

# Study organisational structure

## Operational structure and responsibilities

**Chief Investigator (CI)** – As defined by the NHS Research Governance Framework, the CI is responsible for the design, conduct, co-ordination and management of the study. The CI is responsible for the design management and reporting of the study.

**Study Sponsor – Leeds Teaching Hospitals NHS Trust:** The Sponsor is responsible for study initiation management and financing of the study as defined by Directive

## Financing

This study is supported by the Leeds neurosurgical research fund. JM holds a one year research fellowship award from the Royal College of Surgeons of England.

# Publication policy

The study will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

* + conception and design, or acquisition of data, or analysis and interpretation of data,
  + drafting the article or revising it critically for important intellectual content,
  + and final approval of the version to be published,
  + and that all these conditions must be met (www.icmje.org )

In light of this, the Chief Investigator and other investigators will be named as authors in any publication.

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the analysis of the primary endpoint, either for study publication or oral presentation purposes.

# References

Cleland, J.A., Childs, J.D., Whitman, J.M., 2008. Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. Arch Phys Med Rehabil 89, 69–74. https://doi.org/10.1016/j.apmr.2007.08.126

Cleland, J.A., Fritz, J.M., Whitman, J.M., Palmer, J.A., 2006. The reliability and construct validity of the Neck Disability Index and patient specific functional scale in patients with cervical radiculopathy. Spine 31, 598–602. https://doi.org/10.1097/01.brs.0000201241.90914.22

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, 2nd ed. ed. L. Erlbaum Associates, Hillsdale, N.J.

Fountas, K.N., Kapsalaki, E.Z., Nikolakakos, L.G., Smisson, H.F., Johnston, K.W., Grigorian, A.A., Lee, G.P., Robinson, J.S., 2007. Anterior Cervical Discectomy and Fusion Associated Complications: Spine 32, 2310–2317. https://doi.org/10.1097/BRS.0b013e318154c57e

Freynhagen, R., Baron, R., Gockel, U., Tölle, T.R., 2006. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 22, 1911–1920. https://doi.org/10.1185/030079906X132488

Garrido, B.J., Taha, T.A., Sasso, R.C., 2010. Clinical outcomes of Bryan cervical disc arthroplasty a prospective, randomized, controlled, single site trial with 48-month follow-up. J Spinal Disord Tech 23, 367–371. https://doi.org/10.1097/BSD.0b013e3181bb8568

Hjermstad, M.J., Fayers, P.M., Haugen, D.F., Caraceni, A., Hanks, G.W., Loge, J.H., Fainsinger, R., Aass, N., Kaasa, S., European Palliative Care Research Collaborative (EPCRC), 2011. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 41, 1073–1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016

Kang, Y., Lee, J.W., Koh, Y.H., Hur, S., Kim, S.J., Chai, J.W., Kang, H.S., 2011. New MRI Grading System for the Cervical Canal Stenosis. American Journal of Roentgenology 197, W134–W140. https://doi.org/10.2214/AJR.10.5560

Kundel, H.L., Polansky, M., 2003. Measurement of Observer Agreement. Radiology 228, 303–308. https://doi.org/10.1148/radiol.2282011860

Lawton, C.D., Smith, Z.A., Lam, S.K., Habib, A., Wong, R.H.M., Fessler, R.G., 2014. Clinical outcomes of microendoscopic foraminotomy and decompression in the cervical spine. World Neurosurg 81, 422–427. https://doi.org/10.1016/j.wneu.2012.12.008

Nunley, P.D., Jawahar, A., Kerr, E.J., Cavanaugh, D.A., Howard, C., Brandao, S.M., 2009. Choice of plate may affect outcomes for single versus multilevel ACDF: results of a prospective randomized single-blind trial. Spine J 9, 121–127. https://doi.org/10.1016/j.spinee.2007.11.009

Riddle, D.L., Stratford, P.W., 1998. Use of generic versus region-specific functional status measures on patients with cervical spine disorders. Phys Ther 78, 951–963. https://doi.org/10.1093/ptj/78.9.951

Rodine, R.J., Vernon, H., 2012. Cervical radiculopathy: a systematic review on treatment by spinal manipulation and measurement with the Neck Disability Index. J Can Chiropr Assoc 56, 18–28.

Singh, A.P., 2017. What is ASIA score and how it helps in the classification of spinal injury [WWW Document]. URL http://boneandspine.com/what-is-asia-score-and-how-it-helps-in-classification-of-spinal-injury/ (accessed 6.2.20).

Skovrlj, B., Gologorsky, Y., Haque, R., Fessler, R.G., Qureshi, S.A., 2014. Complications, outcomes, and need for fusion after minimally invasive posterior cervical foraminotomy and microdiscectomy. Spine J 14, 2405–2411. https://doi.org/10.1016/j.spinee.2014.01.048

Stratford, P., 1999. Using the Neck Disability Index to make decisions concerning individual patients. Physiother Can 107–119.

Wainner, R.S., Fritz, J.M., Irrgang, J.J., Boninger, M.L., Delitto, A., Allison, S., 2003. Reliability and diagnostic accuracy of the clinical examination and patient self-report measures for cervical radiculopathy. Spine 28, 52–62. https://doi.org/10.1097/00007632-200301010-00014

Wang, T.Y., Lubelski, D., Abdullah, K.G., Steinmetz, M.P., Benzel, E.C., Mroz, T.E., 2015. Rates of anterior cervical discectomy and fusion after initial posterior cervical foraminotomy. The Spine Journal 15, 971–976. https://doi.org/10.1016/j.spinee.2013.05.042

Westaway, M.D., Stratford, P.W., Binkley, J.M., 1998. The patient-specific functional scale: validation of its use in persons with neck dysfunction. J Orthop Sports Phys Ther 27, 331–338. https://doi.org/10.2519/jospt.1998.27.5.331

Young, B.A., Walker, M.J., Strunce, J.B., Boyles, R.E., Whitman, J.M., Childs, J.D., 2009. Responsiveness of the Neck Disability Index in patients with mechanical neck disorders. Spine J 9, 802–808. https://doi.org/10.1016/j.spinee.2009.06.002

Young, I.A., Cleland, J.A., Michener, L.A., Brown, C., 2010. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil 89, 831–839. https://doi.org/10.1097/PHM.0b013e3181ec98e6

Yousem, D.M., Atlas, S.W., Goldberg, H.I., Grossman, R.I., 1991. Degenerative narrowing of the cervical spine neural foramina: evaluation with high-resolution 3DFT gradient-echo MR imaging. AJNR Am J Neuroradiol 12, 229–236.