

Assessing Cervical Foraminal Stenosis: Volumetric MRI study in Healthy Volunteers

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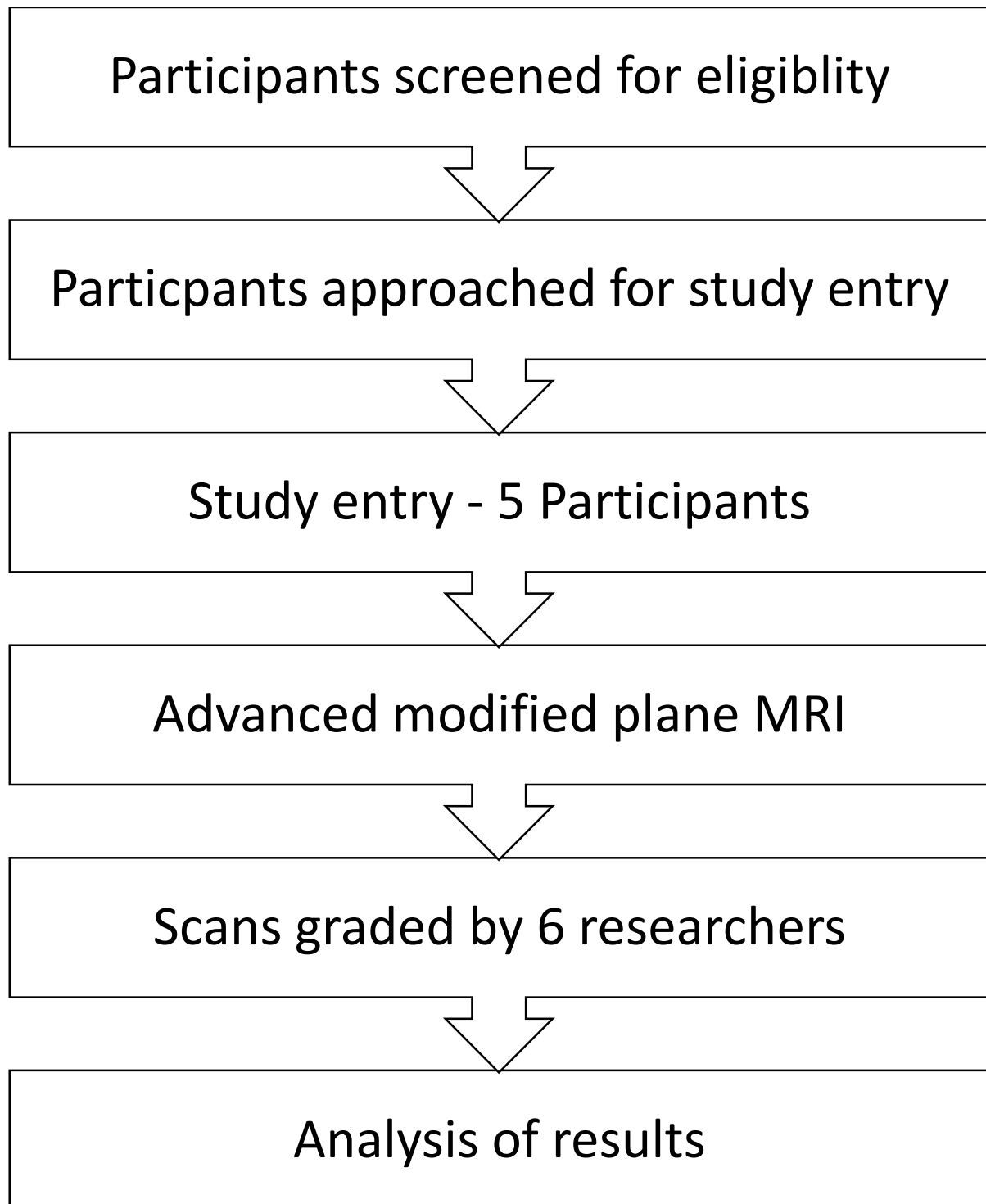
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3 Synopsis

Title	Assessing Cervical Foraminal Stenosis: Volumetric MRI study in Healthy Volunteers
Design	<p>This is a non-randomised single institution feasibility / pilot study to develop a novel imaging technique of the cervical nerve root canal.</p> <p>Healthy volunteers over the age of 40 will be invited to participate. Participants will be recruited from Leeds Teaching Hospital NHS Trust staff.</p> <p>Three-dimensional volumetric data of the cervical spine will be obtained from an MRI scan. The anatomy of the cervical nerve root canal will be analysed to measure areas of nerve root compression using 2 dimensional projections in the plane of the nerve root and with automated computational mathematical modelling.</p>
Aim	<p>Primary Objective: To develop and evaluate the feasibility of advanced MR imaging of the nerve root foramen realigned to the nerve root plane.</p> <p>Secondary Objectives: To develop a scoring system that reflects the type, location, length and severity of root canal stenosis</p> <p>To evaluate the internal and external consistency of the MRI views and established alternative scoring systems</p> <p>Exploratory Objective: To use mathematical modelling techniques to automate the measurement of nerve root canal stenosis</p>
Population:	Healthy Volunteers over the age of 40 recruited from staff members at the Leeds Teaching Hospitals NHS Trust
Number of Participants:	n=5
Inclusion Criteria	<ol style="list-style-type: none"> 1. Age over 40 years 2. Able to provide fully informed written consent 3. Able to lie flat for 1 hour in an MRI scanner 4. Females of childbearing age must be using effective contraception 5. Sufficient understanding of English to participate in the trial
Exclusion Criteria	<ol style="list-style-type: none"> 1. Cervical myelopathy 2. History of cervical trauma 3. Evidence of suspected or histologically proven tumour 4. Previous cervical spine surgery 5. Non-MRI compatible implantable device e.g. pacemaker

	6. Unable to have MRI scan due to Claustrophobia 7. 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

4 Flow diagram



5 Glossary of Terms

Abbreviation	Full expansion
MRI	Magnetic Resonance Imaging
NDI	Neck Disability Index
NHS	National Health Service
ACD	Anterior Cervical Discectomy
PCF	Posterior Cervical Foraminotomy
VAS	Visual Analogue Scale
MDI	Myelopathy Disability Index
SPSS	Statistical package for the social sciences
T	Tesla
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

6 Background

The natural process of aging leads to degenerative changes within the spine including disc prolapse, osteophyte formation, facet joint hypertrophy and ligament 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 particular 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 $\leq 50\%$ 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. In this study we will develop a novel MRI technique, orientated in a modified plane, aligned along and at right angles to the nerve root canal that will optimise assessment of the nerve in the canal. We will also develop a new scoring system and analyse this for internal and external consistency. We will compare the new techniques with the established ones described above.

7 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 therefore rarely used in clinical practice.

We will be using standard MRI techniques in a modified plane 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 will use healthy volunteers to develop the technique – the changes are so common that almost all asymptomatic healthy volunteers over the age of 40 will have some degenerative neck disease.

We will also develop a scoring system based on the modified plane MRI scans and measure its reliability by comparing the scores of 6 different observers. We will measure these variables for the established, published scoring techniques that use standard MRI sequences and we will compare the modified plane MRI scans with standard MRI scans to establish which is better.

Once we have established the optimal way to perform and score these MRI scans, we will be able to build on this project by applying the newly developed techniques to patients being considered for surgical intervention. We expect that the new technique will permit better selection of patients for surgery and inform decisions on whether to perform surgery from the front or from the back of the neck.

8 Aims and Objectives

8.1 Primary Objective

To develop and evaluate the feasibility of advanced MR imaging of the cervical nerve root foramen realigned to the nerve root plane

8.2 Secondary Objectives

To develop a scoring system that reflects the type, location, length and severity of root canal stenosis

To evaluate the internal and external consistency of the new MRI technique and established alternative scoring systems

8.3 Exploratory Objective

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

8.4 Study Null Hypothesis

Modified plane imaging has the same internal consistency as scoring performed on standard axial images

9 Study design

9.1 Summary

This is a non-randomised single institution feasibility / pilot study to develop a novel imaging technique of the cervical nerve root canal.

Healthy volunteers over the age of 40 will be invited to participate. Participants will be recruited from Leeds Teaching Hospital NHS Trust staff.

Three dimensional volumetric data of the cervical spine will be obtained from an MRI scan. The anatomy of the cervical nerve root canal will be analysed to measure areas of nerve root compression using 2 dimensional projections in the plane of the nerve root and with automated mathematical modelling measurements.

9.2 Number of Participants

There will be a total of 5 participants.

10 Eligibility

10.1 Participant eligibility

Eligibility waivers to inclusion or exclusion criteria are not permitted.

10.2 Inclusion Criteria

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

1. Age over 40 years
2. Able to provide fully informed written consent
3. Able to lie flat for 1 hour in an MRI scanner
4. Females of childbearing age must be using effective contraception
5. Sufficient understanding of English to participate in the trial

10.3 Exclusion Criteria

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

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

10.4 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.

11 Recruitment

11.1 Recruitment setting

Participants will be invited from local staff members at Leeds Teaching Hospital NHS Trust to participate in the study. No remuneration will be offered.

Participants will be recruited from Leeds Teaching Hospital Trust research promotion days and through trust email communication. This will include the research patient promotion poster and information leaflet.

11.2 Eligibility screening

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

11.3 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.

11.4 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.

11.5 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.

11.6 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.

12 Data Collection

12.1 Participant information

Information collected will include the following:

- Age, date of birth and initials
- History of symptoms of cervical spine disease
- GP details

12.2 Pre MRI scan limited clinical examination

A limited neurological examination to identify any hidden signs of cervical spine disease will be carried out prior to the MRI scan being performed and this data will be recorded.

Examination data collected will include assessment of sensory function (fine touch and pin prick) in the C4 to T1 dermatomes, motor function in the C4 to T1 myotomes and the following reflexes: biceps, triceps, supinator, knee, ankle and plantar response.

13 Intervention details

13.1 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.

High definition, 3 dimensional cervical spine T1 and 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.

13.2 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

13.3 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.

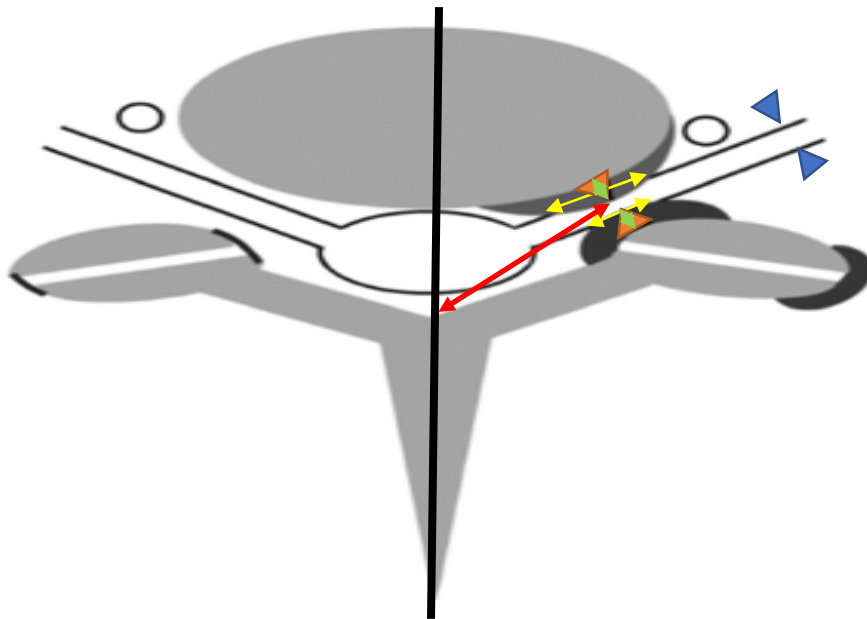
To determine the intra-rater variability the same observer will be given the same images, following a wash out period of one month to reduce bias.

13.4 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)

- a) Measurement of perineural fat obliteration compared to nerve root circumference
- b) 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.

13.5 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.

13.6 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.

14 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.

In the event that a participant withdraws during the MRI scan, their data should be treated as though they had completed the scan, they will not be replaced in the study, they should not be recorded on the non-participation log.

15 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.

15.1 Schedule for data collection

The data collected is summarised in table 1

Events	Eligibility and Registration	Medical Information	MRI data
Study Consent	√		
Clinical data		√	
MRI data collection			√
Safety events	√	√	√

Table 1: Schedule of Events

A medical information CRF will be completed by the clinician and will record the information including, but not limited to:

- Date of Birth, age, initials
- Symptoms of cervical degenerative disease
- Neurological signs of cervical degenerative disease

15.2 Death

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

- Date of death
- Cause of death

15.3 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.

16 Safety reporting

16.1 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.

16.2 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.

16.2.1 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)

16.2.2 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.

16.2.3 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.

16.3 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

16.4 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.

17 Outcome measures

17.1 Primary outcome measure

The measurements that will be made are described in section 13.4 above.

The primary outcome measure is the inter-rater reliability for the Kim grading system. This will be applied to the standard axial images and modified plain images.

Success will be determined if there is a significant improvement in the inter-observer reliability.

17.2 Secondary outcome measures

The secondary outcome measures are

1. The inter-rater reliability for subjective score, Modified Kim Grade, Park Grade, length and laterality of compression.
2. The intra-rater reliability for narrowest diameter, subjective score, Modified Kim Grade, Park Grade, length and laterality of compression.

17.3 Exploratory measures

To explore whether computational mathematical modelling techniques can be utilised to automate the measurement of nerve root canal stenosis by calculating the correlation with the “gold standard” of consultant radiologist assessment for narrowest diameter, Kim grade, Modified Kim Grade, Park Grade, length and laterality of compression

To explore whether diffusion tensor imaging can be utilised to measure the degree of nerve root canal stenosis by calculating the correlation with the “gold standard” of consultant radiologist assessment for narrowest diameter, subjective score, Kim grade, Modified Kim Grade, Park Grade, length and laterality of compression

18 Statistical Considerations

18.1 Sample size

A total of 5 subjects are required. This is a small pilot study to obtain some early data on how best to image the cervical nerve root canals. The data obtained from this study will be used to perform sample size calculations for subsequent studies that will be powered to show significance.

18.2 Planned recruitment rate

Healthy volunteers will be recruited and screened over a 3 month period.

18.3 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 ($\kappa < 0.1$)
 - Slight ($0.1 \leq \kappa \leq 0.2$)
 - Fair ($0.2 < \kappa \leq 0.4$)
 - Moderate ($0.4 < \kappa \leq 0.6$)
 - Substantial ($0.6 < \kappa \leq 0.8$)
 - Nearly perfect ($0.8 < \kappa \leq 1.0$)
- 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.

18.3.1 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 as MRI data collection is at one time point only.

19 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).

20 Quality Assurance and Ethical Considerations

20.1 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).

20.2 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.

20.3 Ethical Approval

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

21 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.

21.1 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.

21.2 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.

22 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

23 Study organisational structure

23.1 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

23.2 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.

24 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.

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