Clinical and Cost-effectiveness of Posterior Cervical Foraminotomy versus Anterior Cervical Discectomy in the Treatment of Cervical Brachialgia: A Multicentre, Phase III, Randomised Controlled Trial (FORVAD Trial)

Version:	3.0
Date:	15/01/2021
Sponsor:	Leeds Teaching Hospitals NHS Foundation Trust
Sponsor Number:	NE14/11401
Funder Ref:	**16/31/53**
REC Ref:	18/NW/0682
IRAS Project ID:	249138
ISRCTN:	ISRCTN10133661

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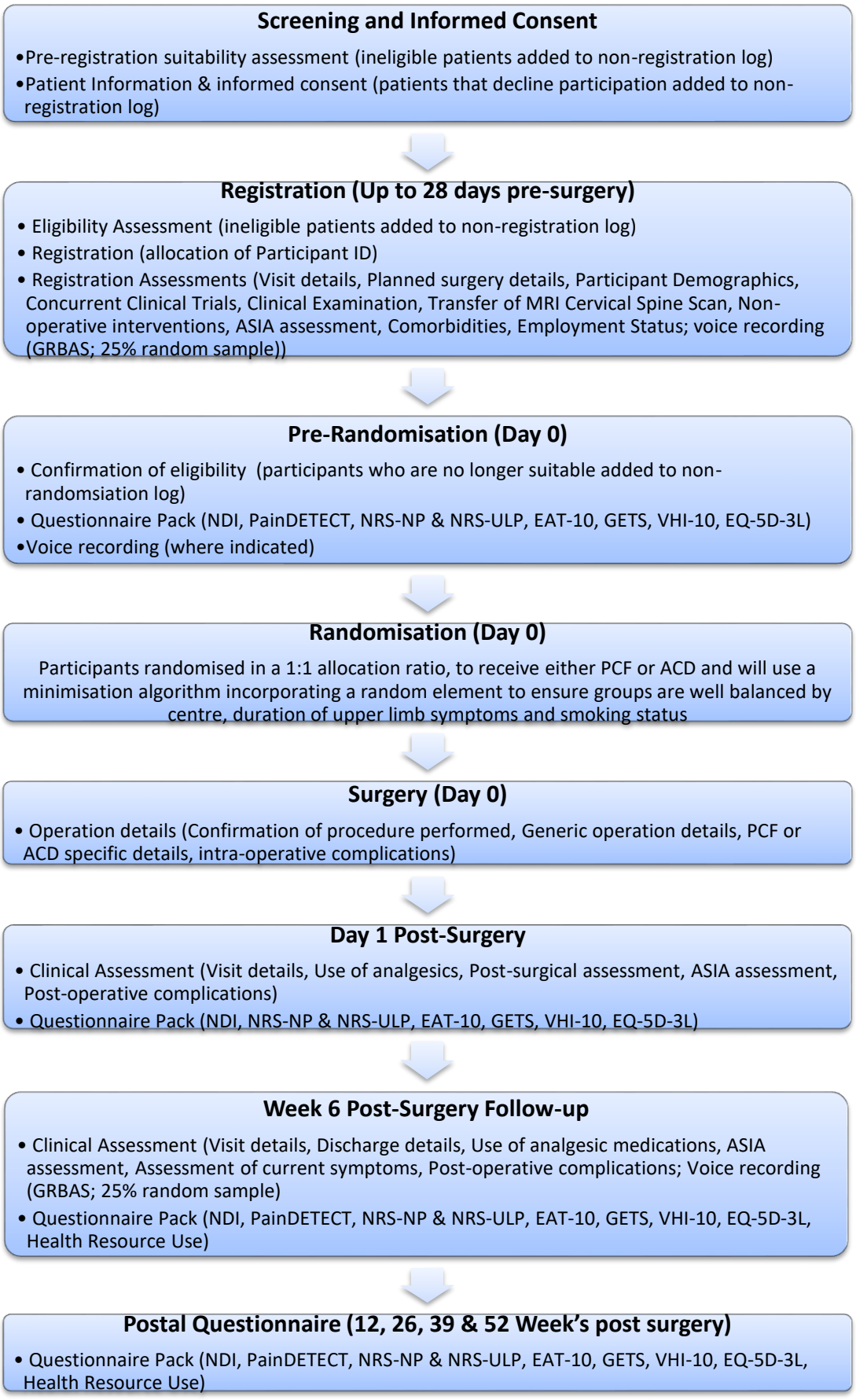
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3. SYNOPSIS

Trial Title	Clinical and Cost-effectiveness of Posterior Cervical Foraminotomy versus Anterior Cervical Discectomy in the Treatment of Cervical Brachialgia: a Multicentre, Phase III, Randomised Controlled Trial
Trial Acronym	**FORVAD**
Trial Design	The trial is a multicentre, Phase III, unblinded, parallel group individually randomised controlled trial (RCT) in patients with symptomatic unilateral cervical brachialgia for at least six weeks secondary to nerve root compression. A total of 252 participants will be recruited. Randomisation will be on a 1:1 allocation ratio to posterior cervical foraminotomy (PCF) or anterior cervical discectomy (ACD). The trial will include a 12 month internal pilot phase to evaluate the feasibility of recruitment and therefore the delivery of the trial.
Trial Aim	To determine the superiority in terms of clinical and cost effectiveness of Posterior Cervical Foraminotomy (PCF) compared to Anterior Cervical Discectomy (ACD) in the treatment of patients with cervical brachialgia. **Primary Objective:** To determine whether PCF is superior to ACD in terms of improving clinical outcome as measured by the Neck Disability Index (NDI) at 52 weeks post–surgery. **Secondary Objectives**: To compare PCF and ACD in terms of: 1. NDI scores over 52 weeks post-surgery 2. Neck and upper limb pain including the shoulder, arm and hand assessed using Numerical Rating Scales, and neuropathic pain (including dysesthetic pain) assessed using the PainDETECT tool over 52 weeks post-surgery 3. Dysphagia (difficulty swallowing) and Globus (sensation of a lump in the throat) over 52 weeks post-surgery as assessed by the participant completed EAT-10 and the Glasgow and Edinburgh Throat Score questionnaires 4. Hoarse voice over 52 weeks post-surgery as assessed by the participant completed Voice Handicap Index-10 and at 6 weeks for

	a sub-set of participants that have a central GRBAS assessment of their recorded voice (see section 12.2) 5. Extent and severity of a patient's spinal cord function, including upper limb nerve root function, using the ASIA score at 1 day and 6 weeks post-surgery 6. Incidence of revision surgery over 52 weeks post-surgery 7. Incidence of surgical complications up to 6 weeks post-surgery 8. Cost-effectiveness over 52 weeks post-surgery **Exploratory objectives:** To explore the impact of variations in the optional surgical components of PCF and ACD on NDI and EQ-5D-3L. The types of variation in the optional surgical components are as follows: a) ACD: Fusion with a cervical plate in addition to anterior cervical discectomy vs simple anterior cervical discectomy without a plate. b) PCF: Posterior cervical minimal access technique (operating using a "tube" system) vs open access technique. To explore the association between pre-operative MRI scan appearances (with regards to position, size and severity of root compression) with pre-operative symptoms and response to surgery**.**
Trial Population:	Patients with symptomatic unilateral cervical brachialgia for at least six weeks with confirmed nerve root compression on MRI imaging or CT myelogram Patients with clinical and / or radiological features of cord compression will be excluded.
Randomisation:	Randomisation will be on a 1:1 allocation ratio to PCF or ACD and will use a minimisation algorithm incorporating a random element, with minimisation factors for centre, duration of upper limb symptoms (6 weeks - < 6 months; ≥ 6 months - < 12 months; ≥ 12 months) and smoking status (smoker or non-smoker, during the last six weeks only).
Trial Intervention:	Patients will be randomised to receive either PCF or ACD.
Study Duration:	All participants will be followed up to 52 weeks post-surgery.
Evaluation of outcome measures	Participants will be assessed at day 1 and weeks 6, 12, 26, 39 and 52 post-surgery

4. FLOW DIAGRAM



5. GLOSSARY OF TERMS

Glossary

ACD	Anterior Cervical Discectomy
ASIA	American Spinal Injury Association
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EAT-10	Eating Assessment Tool-10
EoI	Expression of Interest
GETS	Glasgow & Edinburgh Throat Scale
GP	General Practitioner
GRBAS	Grade, Roughness, Breathiness, Asthenia, Strain scale
HTA	Health Technology Assessment
ICD	Informed Consent Document
ISF	Investigator Site File
MRI	Magnetic Resonance Imaging
NDI	Neck Disability Index
NHS	National Health Service
NIHR	National Institute for Health Research
NRS-NP	Numeric Rating Scale – Neck Pain
NRS-ULP	Numeric Rating Scale – Upper Limb Pain
PI	Principal Investigator
PIS	Patient Information Sheet
PCF	Posterior Cervical Foraminotomy
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework
RN	Research Nurse -When RN is referred to in this protocol it means either the research nurse or someone who has been delegated that duty
SC	Serious Complication
SDV	Source Data Verification
SSOP	Site-Specific Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
USC	Unexpected Serious Complication
VHI-10	Voice Handicap Index-10

6. BACKGROUND

What is brachialgia?

As people age, neck joints can change shape and trap nerves. When a nerve supplying the arm is trapped, neck pain coming down into the arm occurs (cervical brachialgia). Cervical brachialgia is extremely common and debilitating, predominantly affecting people aged 40-60 years old with up to 15% of patients unable to work due to pain (1). In a large registry study (1809 patients), patients had significantly worse scores than the general population in all 8 SF-36 quality of life dimensions (2). The reported incidence of cervical brachialgia is 1.79 cases/1000 per year, with over 110,000 cases of brachialgia per year estimated in the UK. Brachialgia imposes a substantial financial burden on patients and society. In most patients, symptoms are self-resolving with conservative management (analgesia and physiotherapy) however 26% of patients undergo surgery if their symptoms are persistent or remain debilitating (3).

Role of surgery in the treatment of brachialgia

In patients for whom symptoms persist 6 weeks after onset, RCTs have shown that surgery results in a more rapid recovery than further conservative management (4, 5) but which surgical technique to use remains controversial. The current standard operation is anterior cervical discectomy (ACD), accessing the trapped nerve from the front of the neck and removing the whole disc. This is effective but the high incidence of significant, potentially permanent complications including dysphagia (swallowing difficulty) (9.5%) and hoarse voice (3.1%) (6) can be devastating and the high rates of repeat surgery at other neck sites (25.6% risk in 10 years) (7) can prevent complete recovery and delay return to work and normal activities. Management of these complications requires substantial healthcare resources at a high cost to the NHS. There is an age-dependent effect on health-related quality of life, with younger patients of working age most severely affected (2). Thus the impact of complications extends beyond patient health and negatively affects employment and wider social lives.

Posterior cervical foraminotomy

Alternatively posterior cervical foraminotomy (PCF) can be used where surgery is performed from the back of the neck. Only 25% of surgeons perform PCF for brachialgia and the decision on which procedure to use is frequently based on surgeon preference. There is a historical

belief that PCF results in high levels of neck pain, spasms and need for revision surgery (8, 9). However recent studies suggest PCF results in better clinical outcomes (10, 11) and lower complication rates overall compared to ACD (10, 12). These studies did not report high levels of neck pain, spasms or revision surgery with PCF as had been previously thought (10, 12). The amount of neck pain (VAS) following PCF and ACD was in fact reported to be comparable with a study reporting similar median VAS neck scores between PCF and ACD at 3(SD 2.9) and 3(SD 2) (10). ACD and PCF revision surgery rates at the operated spinal level were also comparable in recent studies. In a large retrospective review of 627 ACDs and 163 PCFs, reoperation rates at the index level was 4.8% for the ACD group and 6.4% for the PCF group within 2 years of the initial surgery ($p>0.05$) (13, 14). Hence early beliefs that PCF has more complications now appear unfounded, creating equipoise amongst surgeons as to which is the best operative technique.

Recently there is increasing evidence that PCF may be more effective with fewer complications (it avoids the risk of swallowing difficulty and a hoarse voice) than ACD (10, 11, 15). However to date no RCT directly comparing these techniques has been published, therefore ACD remains the standard procedure for this condition across the UK.

There is a significant gap in the literature on the association between pre-operative MRI scan appearances (with regards to position, size and severity of root compression) with pre-operative symptoms and the response to surgery**.** There are two published scales for assessing the degree of compression on the MRI scan. Park et al (16) used oblique sagittal images to measure stenosis in the root canal, whilst Kim et al (17) have used axial slices. Neither method assessed compression, medial or lateral, to the root canal nor provided clinical correlations with their scales. Furthermore it is unclear whether anterior or posterior compression responds better to an anterior or posterior approach. Utilising the trial data, we will explore and develop understanding of these associations.

Health economics

The average cost of PCF may be lower so that its widespread implementation could lead to significant savings for the NHS. The average cost of PCF is £4,200 pounds and the cost of ACD is £5,380. This is due to ACD normally involving the use of an implant and is therefore more costly by around £1,180 per procedure. If PCF replaced all ACD operations, NHS savings may be in the region of at least £2.1 million per annum, based on 2,500 cervical brachialgia operations per annum in the UK. If the reduction in re-operations due to PCF is

included, savings could be much higher. However these potential cost savings need to be confirmed in a RCT.

In the absence of a well-designed Phase III trial, patients with brachialgia may be sub-optimally managed (via ACD) at a higher cost. This RCT will compare clinical effectiveness, complications and cost–effectiveness of PCF against ACD. Based on our experience and previous trials in this patient population (18, 19), the evidence generated from the proposed trial has the potential to be practice-changing. This will ultimately benefit patients, the NHS and wider society.

Review of literature

Controversy exists over whether ACD or PCF is superior for the treatment of brachialgia. We therefore performed a systematic review by searching PubMed and EMBASE for all studies published on this topic. Studies were included if they met the following criteria: (i) study design: prospective or retrospective comparative studies; (ii) patients with brachialgia due to a lateral disc herniation or foraminal stenosis; (iii) clinical outcomes, radiological outcomes, complications, re-operation rates, and cost effectiveness differences were compared between ACD and PCF; and (iv) published in English. Studies on tumours, trauma, infection, previous surgeries, revision surgeries, combined anterior and posterior surgeries, and other posterior approaches were excluded. Non-English studies were also excluded.

1. *Studies examining the efficacy of ACD or PCF compared with non-surgical interventions in the management of cervical brachialgia*

The efficacy of both ACD and PCF in the treatment of cervical brachialgia is well established. Matz et al 2009 (20) conducted a systematic review of 13 retrospective and 3 prospective studies on the clinical effectiveness of ACD in cervical brachialgia compared with non-surgical interventions. They concluded that ACD provides rapid relief (within 3-4 months) of arm and neck pain, weakness and/or sensory loss. It is more effective than nonsurgical treatments in managing cervical brachialgia. Improvement in motor function at 12 months was also noted.

Heary et al 2009 (21) conducted a systematic review of 13 retrospective studies investigating the effectiveness of PCF compared with non-surgical interventions. Although the studies identified were observational and often lacked validated outcome measures, they concluded that PCF is an effective treatment for cervical brachialgia.

2. *Non-randomised studies comparing ACD and PCF in the management of cervical brachialgia*

Our systematic review identified 6 published non-randomised studies, 4 retrospective and 2 prospective cohort studies, comparing ACD and PCF in the management of patients with cervical brachialgia. These had poor designs including no comparison of preoperative baseline variables to ensure matched groups, small numbers, short follow-up and use of non-validated outcome measures including Odom's criteria that captures only a crude classification of patient outcome as either excellent, good, fair or poor.

The 6 identified studies are briefly described here.

Onimus et al. 1995 (22) compared ACD and PCF in 28 patients (14 in each arm) for treating cervical soft disc herniation using Odom's criteria. At 3 months, 13 of 14 patients in both groups reported excellent/good outcomes.

Korinth et al. 2006 (23) compared 124 ACD and 168 PCF patients over a mean follow-up of 6 years (SD 25.9 months) using Odom's criteria. This non-randomised retrospective study found 93.6% of ACD and 85.1% of PCF patients had excellent/good outcomes ($p<0.05$). Surgery related complications (dysphagia, hoarse voice, transient neurological deficit and post-op haematoma) were observed in 6.5% of ACD and 1.8% of PCF patients (CSF fistula, wound infection and transient neurological deficit) ($p<0.05$).

Tumialan et al. 2010 (24) compared costs and effects of managing unilateral cervical brachialgia with PCF or ACD and fusion in 38 (19 per arm) American military personnel, focusing on time to return to active duty. The ACD and PCF approaches had similar median (SD) operating time (151.8(37) vs 154 (33.6) minutes), median (SD) blood loss (32.6(22) vs 41.3(28.7) mls) and analgesic use but PCF patients returned to unrestricted activity faster (mean 14.8 weeks faster than ACD group, $p<0.001$). The mean direct cost of PCF was $20,094 to $30,553 lower per case than ACD.

Wirth et al. 2000 (12) performed a 3 arm study comparing PCF, ACD patients with fusion and ACD patients with no fusion (14 patients per arm). The proportion of complete or partial pain relief (100% vs 100% vs 96%), requirement for analgesia (15.9 vs 13.0 vs 12.5), median operative time (139 vs 98 vs 120 minutes) and median length of hospital stay (4.3 vs 3.9 vs 4.5 days) were similar in all three groups. All PCF patients and 96% (13 of 14) of the ACD patients reported partial or complete relief of radicular pain ($p=0.78$).

Herkowitz et al. 1990 (25) compared outcomes in 28 ACD and 16 PCF patients with mean follow-up of 4.2 years using Odom's criteria. Good/excellent results were obtained in 95% (26 of 28) of ACD and 75% (12 of 16) of PCF patients (P=0.55).

Considering the above limitations our group at Leeds recently published local experience comparing 150 ACDs and 51 PCFs in a retrospective study (10). It is the first study in the literature to compare both arms using a validated outcome measure (NDI). PCF delivered a better median NDI improvement of 21.9% (SD 21.8%) compared to ACD which delivered a median improvement of 11.9% (SD 22.7%). The observed 10% difference (SD 23%) in the NDI score was in favour of PCF.

Since our publication, recently Alvin et al 2016 (15) conducted a one year retrospective study to compare the clinical and cost-effectiveness of ACD compared to PCF to treat patients with brachialgia. The authors found no difference on visual analogue scale (VAS score), EQ-5D and Pain Disability Questionnaires between both treatment arms (p=0.40, p=0.60 and 0.50 respectively); However it is important to note that reliability and validity of these outcome measures have not been tested in patients with brachialgia. The authors nevertheless found PCF to be more cost-effective than ACD (see point 4. *Studies comparing cost-effectiveness of ACD v PCF* below).

3. *RCTs of ACD v PCF*

There are no published RCTs comparing ACD and PCF. In June 2013, an RCT comparing PCF and ACD for foraminal stenosis of the cervical spine (ForaC trial) (26) began recruiting across two centres in Austria. The primary outcome is NDI at 5 years post-surgery. The planned sample size is 88 patients based on disc replacement trials. Our power calculation based on local audit data (10) suggests that the trial is underpowered for detecting the minimum clinically important difference and will not provide the range of outcomes that would impact policy decisions in the NHS.

There has been one published RCT comparing ACD with endoscopic (minimally-invasive) PCF(27). In this single-centre study conducted in Germany the authors compared the outcome of 175 patients and found no difference between treatment arms. The outcome measures used were the VAS score arm pain (VAS-AP), German version North American Spine Society (NASS) Instrument and Hilibrand Criteria. Mean VAS-AP scores at 12 months for ACD and PCF were 7 and 8 (p>0.05) respectively. The NASS instrument measure scores were 1.7 and 1.8 for ACD and PCF respectively. Finally the proportion who reported excellent results based

on the Hillibrand criteria were 78% and 80% for ACD and PCF respectively. This study has several limitations. Firstly, a power calculation was not reported. Moreover non-validated outcome measures were used; including the NASS instrument which has been shown to have poor reliability and validity in assessing outcomes of brachialgia patients(28). Furthermore, in the UK as well as worldwide, the vast majority of PCF (>98%) are performed using the standard open technique therefore it is difficult to extrapolate the findings of this trial to UK practice. Finally, the study included patients who have had symptoms for only 5 days whereas in the UK it is standard practice, based on clinical evidence (3, 5), to recommend surgery following a 6 week period of conservative management.

4. *Studies comparing cost-effectiveness of ACD v PCF*

Alvin et al 2016 performed a retrospective 1-year cost-utility analysis on 45 patients to determine the cost-effectiveness of ACD in comparison to PCF for patients with single-level cervical radiculopathy. The authors found PCF to be less costly ($12,777 vs. $18,473) and more effective (0.16 vs 0.14 increase in QALYs over 1 year) than ACD, supporting the hypothesis that PCF is cheaper and more effective in improving health-related outcomes than ACD (15). This retrospective study provides evidence that the NHS savings by replacing ACD with PCF may be substantial.

All the above existing data comparing the techniques are from small, single-centre, retrospective studies limited by poor design and assessed as class III evidence (North American Spine Society Classification). Hence it is not surprising that systematic reviews by Heary et al. 2009 and Matz et al. 2009 (20, 21) as well as a review article on cervical brachialgia in the New England Journal of Medicine in 2005 (3) have all called for an RCT to compare these procedures.

Until recently, there were no studies that created a sense of equipoise in the surgical community that would enable a RCT to be conducted. However, in 2015, the first study comparing both techniques using validated outcome measures was published by our group in Leeds, UK(10). This study of 201 patients was important as it created a position of equipoise amongst surgeons in the UK and beyond. This is evidenced by our survey of 18 UK centres (50 Neurosurgeons) highlighting considerable support for our trial (29). The results of the survey report that clinical experts including neurosurgeons are in support of the research question and are enthusiastic about taking part. Thus, the current climate of equipoise and support in the surgical community provides a good opportunity to conduct an RCT now in order to determine the superior surgical procedure for the treatment of brachialgia.

Following our publication, The Society of British Neurological Surgeons, which represents over 150 neurosurgeons in the UK, has highlighted this question as a key research topic (http://www.sbns.org.uk/index.php/research/advertisement-for-clinical-trials/). Having reviewed the above literature and our publication, the society is supporting our proposal to conduct an RCT comparing PCF with ACD in patients with cervical brachialgia.

A systematic review was recently published on this topic also calling for a RCT to be conducted and therefore supporting our grant application(30). In the review of all the above publications comparing both treatment arms, the authors reported no difference between PCF and ACD in the treatment of brachialgia, with no increased complication and re-operation rates. Nevertheless, there was a trend favouring PCF with a risk ratio of 1.53 (CI 0.84-2.79) indicating a (non-significant) increased risk of complications for the ACD group. It is worth noting that a significant proportion of the patients from the review were from studies using retrospective data and utilising various, often un-validated, outcome measures. Using NDI as an outcome measure, Selvanathan et al 2015 (10) have demonstrated a trend favouring PCF in a non-randomised retrospective study limited by a type 2 error. A well conducted appropriately powered multicentre RCT is likely to demonstrate the superiority of PCF. In terms of health economics, both the groups of authors reported PCF may have lower medical costs than ACD and may reduce the need for further surgery. Based on the available evidence, both groups of authors concluded that PCF is an alternative surgical procedure in the treatment of brachialgia.

Finally, there is potential financial benefit to conduct the proposed trial as it may lead to major NHS cost savings. Given the incidence of cervical brachialgia patients requiring surgical intervention, the current financial burden on the NHS, and the paucity of data demonstrating clinical and cost effectiveness and adverse outcomes, a definitive trial of PCF versus ACD is timely.

7. AIMS AND OBJECTIVES

The aim of the study is to determine the clinical and cost effectiveness of Posterior Cervical Foraminotomy (PCF) compared to Anterior Cervical Discectomy (ACD) in the treatment of patients with cervical brachialgia.

7.1 PRIMARY OBJECTIVE

To determine whether PCF is superior to ACD in terms of improving clinical outcome as measured by the Neck Disability Index (NDI) at 52 weeks post–surgery.

7.2 SECONDARY OBJECTIVES

To compare PCF and ACD in terms of:

1. NDI scores over 52 weeks post-surgery
2. Neck and upper limb pain including the shoulder, arm and hand assessed using Numerical Rating Scales, and neuropathic pain (including dysesthetic pain) assessed using the PainDETECT tool over 52 weeks post-surgery
3. Dysphagia (difficulty swallowing) and Globus (sensation of a lump in the throat) over 52 weeks post-surgery as assessed by the participant completed EAT-10 and the Glasgow and Edinburgh Throat Score questionnaires
4. Hoarse voice over 52 weeks post-surgery as assessed by the participant completed Voice Handicap Index-10 and at 6 weeks for a sub-set of participants that have a central GRBAS assessment of their recorded voice.
5. Extent and severity of a patient's spinal cord functional impairment, including upper limb nerve root function, using the ASIA score at 1 day and 6 weeks post-surgery
6. Incidence of revision surgery over 52 weeks post-surgery
7. Incidence of surgical complications up to 6 weeks post-surgery
8. Cost-effectiveness over 52 weeks post-surgery

7.3 EXPLORATORY OBJECTIVES

1. To explore the impact of variations in the optional surgical components of PCF and ACD on NDI and EQ-5D-3L. The types of variation in the optional surgical components are as follows:

   a) ACD: Fusion with a cervical plate in addition to anterior cervical discectomy vs simple anterior cervical discectomy without a plate.

   b) PCF: Posterior cervical minimal access technique (operating using a "tube" system) vs open access technique.

2. To explore the association of pre-operative MRI scan appearances (with regards to position, size and severity of root compression) with pre-operative symptoms and response to surgery.

8. TRIAL DESIGN

8.1 SUMMARY

The trial is a multicentre, Phase III, unblinded parallel group, superiority, individually randomised controlled trial (RCT) in patients with symptomatic unilateral cervical brachialgia for at least six weeks with confirmed nerve root compression on MRI imaging or CT myelogram.

A total of 252 participants will be randomised. Randomisation will be on a 1:1 allocation ratio to PCF or ACD and will use a minimisation algorithm incorporating a random element, with minimisation factors for centre, duration of upper limb symptoms and smoking status.

The trial will not be blinded to participants, medical staff, or clinical trial staff.

8.2 INTERNAL PILOT

The trial will include an internal pilot phase to evaluate the feasibility of recruitment within the planned timelines, based on the number of actively recruiting sites and overall average recruitment rate/site/month. The pilot will also assess early safety data, data validity, compliance with study procedures, compliance and completeness of patient completed quality of life questionnaires, eligibility of the clinical teams and type of procedure performed (e.g. minimal access or open surgery).

9. ELIGIBILITY

9.1 RESEARCH SITE ELIGIBILITY

The trial will open in at least 10 sites. Each site must fulfil a set of pre-specified criteria and complete a registration form which verifies that the research site is willing and able to comply with the trial requirements. Research sites will be required to obtain local management approval, return all required essential documentation to CTRU and undertake a site initiation with the CTRU prior to the start of recruitment into the trial.

Participation of research sites will be dependent upon the following criteria:

1) Site must be able to perform both anterior cervical discectomy (ACD) and posterior cervical foraminotomy (PCF)
2) Have the capacity to recruit at least 10 patients per year.

9.2 SURGEON ELIGIBILITY

Prior to participating in the trial, surgeons must be able to:

- Confirm that they have performed at least 10 anterior cervical discectomy and 10 posterior cervical foraminotomy cases as the primary surgeon.
- Complete the e-learning package (see below)

9.2.1 E-learning:

The e-learning package is accessible through the ebrain platform (http://www.ebrain.net). This includes a review of the literature and the trial protocol. The techniques of anterior cervical discectomy and posterior cervical foraminotomy are also included.

9.2.2 Surgeon procedure experience

Surgeon experience level at the point of entry into the trial will be recorded, in addition to ongoing collection of surgeon experience throughout the trial (including relevant experience gained outside of the trial).

9.3 PATIENT ELIGIBILITY

Eligibility waivers to inclusion or exclusion criteria are not permitted.

9.3.1 Inclusion Criteria

Patients will be eligible for registration on to the trial if they fulfil the following inclusion criteria:

1) Aged ≥18 years old
2) Diagnosis of unilateral cervical brachialgia as confirmed by MRI or CT myelogram taken within the last 12 months
3) Symptoms of cervical brachialgia present for at least 6 weeks
4) Single level nerve entrapment
5) Postero-lateral disc and/or foraminal narrowing
6) Failed conservative management (including but not limited to; medication, physiotherapy, modification of daily activities)
7) Able and willing to comply with the terms of the protocol, including QoL questionnaires (QoL questionnaires are provided in English only, for this reason patients must be English speaking)
8) Able to provide written informed consent

9.3.2 Exclusion Criteria

1) Cervical disc causing cord compression
2) Cervical myelopathy
3) Bilateral cervical brachialgia
4) Previous cervical spine surgery
5) Professionals where a hoarse voice would be exceptionally significant (e.g. singers or speakers)
6) Skin disease at surgical sites (e.g. eczema)
7) Pregnancy
8) Cervical deformity
9) Not suitable for anterior cervical discectomy (ACD)
10) Not suitable for posterior cervical foraminotomy (PCF)

9.3.3 Concurrent Clinical Trials

To avoid potential confounding issues, ideally patients should not be recruited into other trials. Where recruitment into another trial is considered to be appropriate and unlikely to have any detrimental effect on the FORVAD trial this must first be discussed with the CTRU who will contact the Chief Investigator.

10. RECRUITMENT

10.1 RECRUITMENT SETTING

Patients will be recruited from standard secondary care neurosurgical centres in the UK following referral for cervical brachialgia by their General Practitioner.

10.2 ELIGIBILITY SCREENING

Participating research sites will be required to complete a non-registration log for all those patients presenting to a participating surgeons clinic with a diagnosis of cervical radiculopathy excluding myelopathy who have been considered for the trial but have not been registered into the study. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Non-registration logs should be returned to the CTRU on a monthly basis. The following anonymised information will be collected:

- Date screened
- Age
- Gender
- Duration of upper limb symptoms
- Smoking status
- The reason not eligible for study participation OR
- The reason eligible but declined

10.3 INFORMED CONSENT

All patients with cervical radiculopathy referred for surgery without myelopathy and attending a participating surgeon's clinics will be considered as potentially eligible for this study.

Potential participants will be identified while attending a standard secondary/tertiary care neurosurgical outpatient clinic.

Suitability for inclusion into the trial will be assessed according to the eligibility criteria and patients will be provided with verbal and written details about the trial (FORVAD Patient Information Sheet/Informed Consent Document PIS/ICD) by a member of the attending clinical team. This will include detailed information about the rationale, design and personal implications of the study.

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

Assenting patients will be formally assessed for eligibility and invited to perform written informed consent for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the Principal Investigator (PI) or an appropriate, delegated, healthcare professional. The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site 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.

Patients who decide they would like to take part in the trial will be invited for formal eligibility assessment, consent, registration and pre-operative baseline clinical assessments. Informed, written consent must be obtained prior to registration and prior to the participant undergoing procedures that are specifically for the purposes of the trial and are not standard routine care at the participating sites (including the collection of identifiable participant data).

A record of the consent process detailing the date of consent and all those present will be detailed in the participant's hospital notes. The original consent form will be filed in the Investigator Site File at the hospital. A copy of the consent form will be given to the participant, a second copy filed in the hospital notes (as per local practice) and a third copy will be returned to the CTRU at the University of Leeds.

Where a participant is required to re-consent or new information needs to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

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

10.3.1 Timing of consent

Written informed consent should be obtained as close to registration as possible and must be no more than 28 days before registration.

10.3.2 Loss of capacity

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

10.4 REGISTRATION

Informed written consent for entry into the trial must be obtained prior to registration.

10.4.1 Timing of registration

Registration should take place as soon as possible after consent is obtained. Registration should be at least one day and no more than 28 days prior to the planned surgery date.

10.4.2 Registration process

At the point of registration participants will be issued a unique trial number. This unique five digit number together with the centre number will form the participant ID number. Please note this unique ID number will be required to complete the informed consent form.

Registration will be performed using either the 24-hour automated registration telephone system or via a web address based at the CTRU. For the telephone system, a site code, authorisation code and PIN will be required. To register using the web address a staff site email address, a site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

The person telephoning or accessing the web address to register the participant must have the completed Registration Case Report Form (CRF) available at the time of registration as the following additional information will be required:

- Site Code
- Participant details, including initials and date of birth
- Confirmation of eligibility

- Confirmation of written informed consent

Direct line for 24-hour registration: 0113 343 2290

Web address for 24-hour registration: https://lictr.leeds.ac.uk/webrand/

Participants may only be registered into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log.

Note that 25% of patients will be randomly selected at registration to provide voice recordings for assessment with the GRBAS tool. Please refer to section 12.2 for further details.

After trial registration the research site will:

- Add the unique participant ID number to all CRFs and participant consent and contact details forms.
- Return a copy of the completed consent and contact details forms to CTRU
- Complete the Registration assessments (section 12.3, including the additional voice recording for selected participants) and eligibility checklist
- Book the surgery and advise the patient of the date of planned surgery. Surgery should take place within 28 days of registration.

Following participant registration, CTRU will email a Participant Registration Notification to the research site.

10.5 NON-RANDOMISATION:

Participants who have been registered will be assessed on the day of surgery to confirm that they are still eligible to be randomised into the trial. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Non-randomisation logs should be returned to the CTRU on a monthly basis. The following information will be collected:

- Site code
- Participant's unique trial number provided at registration

- The reason not eligible for randomisation OR
- The reason participant declined to proceed to randomisation OR
- Any other reason randomisation was not performed

10.6 RANDOMISATION:

10.6.1 Timing of randomisation

Participants who have previously been registered, have confirmation of eligibility and written informed consent will be randomised into the trial by an authorised member of staff at the trial research site on the day of the patient's surgery. Participants must complete the participant questionnaire booklet prior to randomisation (see section 12.4).

10.6.2 Randomisation process

Randomisation will be performed centrally using the CTRU automated secure 24-hour randomisation service which can be accessed via the web or telephone. For web and telephone randomisation, the same site code, authorisation code/site staff email address and PIN used for registration (refer to section 10.4.2) provided by CTRU, will be required to access this system. The person telephoning or accessing the web address to randomise the participant must have the completed Randomisation CRF available at the time of telephoning/accessing the web, as the following information will be required:

- Site code
- Participant's unique trial number provided at registration
- Participant's date of birth
- Confirmation of completion of the registration assessment (including the additional voice recording where applicable)
- Confirmation of participant's eligibility for the trial
- Confirmation of completion of the pre-operative participant questionnaire booklet
- Confirmation that the participant's surgery is planned for the day of randomisation
- Stratification factors: duration of upper limb symptoms, smoking status (see section 10.6.3)
- For participants that are current smokers: number of cigarettes per day on average over the last six weeks

10.6.3 Treatment allocation

Participants will be randomised in a 1:1 allocation ratio, to receive either PCF or ACD and will use a minimisation algorithm incorporating a random element to ensure groups are well

balanced for the following participant characteristics, details of which will also be required for randomisation:

- Centre
- Duration of upper limb symptoms: 6 weeks to < 6 months; ≥ 6 months to < 12 months; ≥ 12 months
- Smoking status in the last 6 weeks (non-smoker, smoker)

Direct line for 24-hour randomisation: 0113 343 2290
Web address for 24-hour randomisation:
https://lictr.leeds.ac.uk/webrand/

After trial randomisation the research site will:

- Ensure that participants are notified of their appointment dates.
- Notify the participant's GP of their participation in the trial using the approved FORVAD GP Letter.

Following participant randomisation, CTRU will email a Participant Randomisation Notification to the research site.

11. INTERVENTION DETAILS

11.1 PRE-OPERATIVE INVESTIGATIONS AND PREPARATION

Pre-operative investigations and preparation will be as per individual site protocol.

11.1.1 Restricted ASIA assessment

All participants will undergo a restricted ASIA assessment as part of their registration assessments (which should be carried out pre-operatively within 28 days of surgery). The patient's score will be 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. Sensory assessment will be restricted to the following regions only: C4, C5, C6, C7, C8, T1, T10, L2, L4 and S1. The sensory assessment will be performed twice for each area, once using light-touch sensation and once using pin-prick sensation. Motor function will be assessed across

all 20 muscles. Please refer to section 14.2 for further details regarding scoring for this assessment.

11.1.2 Voice recording sample

Those participants randomly selected at registration to undergo an additional assessment of hoarse voice will provide a recording of their voice as part of their registration assessments (which should be carried out pre-operatively within 28 days of surgery). Details of this assessment can be found in appendix 1. Participants must be asked whether or not they consider their voice to be “normal” at the time the recording is performed. If a participant indicates that their voice is not “normal”, the recording should still be taken as part of the registration assessments, and an additional recording should take place as per section 11.2.1. Recordings should only be sent to CTRU for central review once randomisation into the trial has taken place.

11.2 DAY OF SURGERY

11.2.1 Voice recording sample

Those participants randomly selected at registration to undergo an additional assessment of hoarse voice, and who indicated that they did not consider their voice to be “normal” at the time of the recording taken as part of the registration assessments, will be asked to provide a further recording of their voice. This recording will take place prior to randomisation on the day of surgery. Participants will be asked whether or not they consider their voice to be “normal” at the time the recording is performed. All recordings should be sent to CTRU for central review.

11.2.2 Posterior Cervical Foraminotomy (PCF):

Participants randomised to receive PCF only.

PCF is an operative technique that is used to treat patients with cervical brachialgia with evidence of nerve root compression on imaging. It is utilised to decompress the exiting nerve root from a posterior approach without destabilising the cervical spine. PCF allows wider exposure of the exiting nerve root compared to anterior approaches and does not destabilise the spine therefore avoiding the need for fusion. The technique also avoids anterior approach related morbidity including damage to the oesophagus, carotid sheath, and recurrent laryngeal nerve.

<u>Prior to the skin incision</u>

Mandatory

Prior to surgery, clinical assessment and imaging with MRI or cervical myelography must be used to identify the location of the affected nerve root and correlate this with the clinical level as well as confirm absence of cord compression and myelopathy.

Under general anaesthesia, the participant is positioned in a prone position. A Mayfield™ pin headrest is used to secure the head in a flexed position; an alternative headrest that can be used is the Sugita™ head frame.

Intra-operative localisation of the spinal level to be operated on is obtained using fluoroscopy prior to an incision being made. This ensures the incision is correctly placed and not too long. Unless contraindicated, skin preparation should be with an alcoholic skin prep agent, care must be taken to avoid alcoholic skin preparations from running round into the eyes. Local anaesthetic with adrenalin is used at the incision site.

Incision and exposure

Option A: traditional open foraminotomy

A midline dorsal incision is made overlying the spinal level of interest. The incision should be kept as short as possible to minimise post-operative neck pain. The incision is deepened until the spinous processes are reached. Subperiosteal dissection is continued unilaterally to expose the spinous processes, lateral mass and lamina above and below the level to be decompressed. A subperiosteal route protects the muscles which can be a source of post-operative pain, excessive use of monopolar diathermy should also be avoided. Once the laminae and lateral masses have been exposed fluoroscopy is again employed to confirm the correct level. A cranked retractor system such as a Blackbelt™, Caspar™ or McCulloch™ retractor is used to allow surgical access whilst minimising the size of the wound.

Option B: minimal access technique

A minimally invasive ‘tube based’ approach is permitted whereby a 2cm skin incision is made 2.5cm lateral to the spinous process with fluoroscopic guidance. Two planar x-rays must be used for docking the dilators on the lateral mass to avoid the known risk of perforation of the ligamentum flavum with the dilators. The muscle fascia is opened and progressive dilators are directed obliquely under fluoroscopy through the muscle fibres to the facet. After radiographically confirming the two laminae at the level of the pathology, the muscle attachments are coagulated to complete the exposure. The laminae and lateral masses are defined as specified in the standard open approach above.

Decompression

Mandatory

Bone removal begins using small kerrison punches and / or a high speed drill to thin the inferior edge of the superior lamina and the superior aspect of the inferior lamina. No more than 50% of the lateral mass should be removed. Care must be taken to adequately decompress the nerve root without compromising spinal stability. A thin foot plate (usually 1mm or maximum 2 mm) Kerrison™ punch may be used to dissect the bone off the ligamentum flavum and the nerve underlying it. Instruments with a thick footplate should be avoided as their insertion may cause further compression and damage the nerve. The ligamentum flavum is also removed and this removal of the ligamentum flavum can proceed laterally until the lateral dural sac and the nerve root with its axilla are exposed. Adequate decompression of the neural foramen may be evaluated by very careful palpation using a nerve hook.

Optional

The nerve root axilla may be explored to expose an osteophyte or soft disc which may then be removed.

Haemostasis

Mandatory

After decompression the wound will be copiously irrigated, followed by meticulous haemostasis. Excessive coagulation of epidural vessels around the nerve root should be avoided.

Closure

Mandatory

The wound is then closed in layers with muscles, fascia, then subcutaneous tissue, and finally skin. The choice of materials used to close the wound are according to surgeon preference.

Optional

A drain may be used according to surgeon preference.

Post-op care

Mandatory

Post-operatively, routine activity may be resumed, as pain allows. No post-operative imaging is needed unless the participant develops a new neurological deficit. Participants are expected to be discharged the following day after physiotherapy review.

11.2.3 Anterior Cervical Discectomy (ACD):

Participants randomised to receive ACD only.

ACD is used in brachialgia to decompress the nerve root affected by a disc or osteophytic spur via an anterior approach. Prior to surgery clinical assessment and imaging with MRI or cervical myelography is used to correlate the location of the brachialgia with the affected nerve root.

Prior to skin incision

Mandatory

Prior to surgery, clinical assessment and imaging with MRI or cervical myelography is used to identify the location of the affected nerve root and correlate this with the clinical level as well as confirm the absence of cord compression or myelopathy.

The participant is positioned in a supine position with the neck in extension, a roll is placed behind the scapulae. The shoulders may be depressed using tape for better visualisation of the lower cervical vertebrae on fluoroscopy.

The approach is most commonly performed from the right hand side but the left side may be used according to a surgeon preference. The participant is placed in the supine position on a head ring or horse shoe. Depending on the surgeon's preference, pre-operative traction may be used. If not used, intra-operative disc spreading or pin retractors may be used.

Pre-operative confirmation of the operative level may be obtained using fluoroscopy to localise the level of the incision. Anatomical landmarks (mandible, hyoid bone, thyroid and cricoid cartilage) may also be used to localise the level of the incision.

Incision

Mandatory

A transverse horizontal incision following a skin crease is made from the medial border of the sternocleidomastoid muscle and approaching the midline.

Exposure

Mandatory

Once the skin incision is performed, the platysma muscle may then be divided horizontally or split vertically. The platysma muscle is elevated at both wound margins and dissection proceeds immediately beneath this muscle.

The approach is on the medial edge of the sternocleidomastoid muscle. This plane is followed to the carotid sheath. Once the carotid artery has been palpated, the trachea/larynx and oesophagus/pharynx are retracted medially. Once this has been performed the prevertebral fascia becomes visible and is divided in the midline.

The longus colli muscles overlying the anterolateral edge of the vertebral bodies and discs are then visualised. The affected level thought to be appropriate is selected and verified with fluoroscopy.

Once the correct level has been confirmed the longus colli muscles are raised bilaterally from the anterior surface of the two vertebral bodies adjacent to the interspace that will be explored. A self-retaining anterior spinal retractor is then inserted underneath the longus colli muscles bilaterally. A window is made into the disc interspace with an 11 blade and extended laterally to the unco-vertebral joint.

Resection

Mandatory

An operating microscope is used. The superficial disc material is resected with cervical curettes and rongeurs. For the deeper portion of the discectomy, a high speed drill is used especially where there are posterior osteophytes that need to be removed. Care should be taken to avoid damaging the bony end plate in the anterior 2/3rds of the vertebral bodies. The posterior longitudinal ligament is divided across the entire width of the interspace. The neural foramen is opened to ensure that the nerve root has been decompressed. The medial edge of the nerve root should be visualised and decompression can be assessed using a blunt hook. Excessive use of bipolar and haemostatic agents that expand should be avoided.

Insertion of an implant

Mandatory

Once the discectomy and appropriate bony decompression has been completed, the height of the disc space is obtained by measurement with an interbody spacer and a cage, iliac crest graft or no implant is inserted according to a surgeon's usual practice. An artificial disc replacement is not permitted in this trial. A cage may be packed with some bone matrix or

other bone substitute to promote fusion. The choice of cage/spacer or fusion material is at the discretion of the operating surgeon.

Optional

An anterior cervical plate (made from titanium or resorbable plastic polymer) of adequate length to span the fusion area may be used. The type of plate and screw system used is at the discretion of the surgeon.

Haemostasis and closure

Mandatory

The participant's carotid pulse is verified and superficial bleeding is controlled with bipolar cauterisation. The platysma and skin are closed. The choice of materials used to close the wound are according to surgeon preference.

Optional

A surgical drain may be used.

Post-operative care

Mandatory

Post-operatively the participant can mobilise immediately as pain allows. If used the drain is removed the following day. Unless the participant develops a new neurological deficit, post-operative imaging is not mandatory but some surgeons may elect to perform AP and lateral x-rays. Participants are normally discharged the following day after physiotherapy review.

11.3 ADDITIONAL TREATMENTS:

During the course of follow up participants may require further intervention for brachialgia as per routine NHS practice. Further clinical intervention is permitted for participants. If a participant receives additional treatment, information on the type of intervention (e.g. PCF or ACD), the details of the treatment received and the reason will be collected.

11.4 CONCOMITANT TREATMENTS:

Concomitant treatments and medications include physiotherapy, chiropractor, analgesics (NSAIDS, paracetamol, neuromodulating agents and/ or opioids) and cervical root injections.

Decisions about concomitant medications/treatments will depend on the local medical plan and clinical management. Details of concomitant treatments and medication will be collected on the clinical post-operative assessment CRFs completed at Day 1 and Week 6 post-surgery and on the Health Resource Use questionnaire. In the event of a Serious Complication, concomitant treatment medication will be captured on a Serious Complications CRF (see section 13).

11.5 POST-OPERATIVE CARE

Post-operative care will be as per site protocol.

11.5.1 Clinical Assessments

Participants must be reviewed at:

- 1 day post operation
- 6 weeks post operation.

Participants will undergo the restricted ASIA assessment described in section 11.1.1 and complete a quality of life questionnaire booklet at each of these visits (see section 12). Additionally, those participants randomly selected at registration to undergo an additional assessment of hoarse voice will be asked to provide a recording of their voice at 6 weeks post-operation (see appendix 1). Participants are not required to indicate whether or not they consider their voice to be “normal” at this time.

Any further visits will be according to local standard clinical practice.

11.6 WITHDRAWAL OF TREATMENT/INTERVENTION

Clinicians involved in the trial should not withdraw participants from the trial 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 randomisation, no further data is required to be submitted. In the event that a participant withdraws after randomisation but prior to their operation, collection of follow-up data will still be required. For participants withdrawing from

the trial after their operation, they will still attend follow-up visits unless unwilling to do so and safety data and follow-up data will continue to be collected.

The PI or delegate must make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal Request CRF in order that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

12. DATA COLLECTION

Participating research sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial. The CRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials. Clinical data will be collected at registration, on the day of surgery and at 1 day and 6 weeks post-surgery; participant completed data will be collected at pre-operative baseline assessment (day 0) and at 1 day, 6, 12, 26, 39 and 52 weeks post-surgery.

The pre-operative MRI scan or the myelogram of the cervical of randomisation needs to be sent to the CTRU following randomisation. For full details of the imaging requirements and process please refer to the relevant SSOP in the Investigator Site File (ISF).

For those participants required to provide a voice recording, the recordings will be taken at registration and indication should be given as to whether the participant's voice is their "normal voice" at the time of recording. If the participant's voice is not considered to be "normal", the recording should still be performed at registration, but should be repeated on the day of surgery prior to randomisation. Recordings should also be taken at the Week 6 follow-up assessment visit and all recordings sent to the CTRU. For full details of the voice recording requirements and process please refer to the relevant SSOP in the ISF.

12.1 SUBMISSION OF TRIAL DATA

Participating research sites will be expected to submit original paper CRFs to the CTRU at the University of Leeds and retain copies of all completed CRFs for the trial in the Investigator Site File. Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant

data. Any outstanding CRFs will be chased by the CTRU until received or until the data is confirmed as unavailable.

12.2 SCHEDULE OF CLINICAL ASSESSMENTS/DATA COLLECTION POINTS

The timing of clinical assessments and data collection points are summarised in Table 1. Participants will be followed up as per protocol via clinic visits until 6 weeks post-surgery and by postal questionnaires until 52 weeks post-surgery.

Table 1: Schedule of Events: Clinical Assessments

Events	Registration (Up to 28 days pre-surgery)	Randomisation /Surgery (Day 0)	Post-surgery follow-up (Day 1)	Post-surgery follow-up (Week 6)
Trial Consent	√			
Registration	√			
Clinical examination	√			
Demographics	√			
Use of analgesics	√		√	√
Non-operative interventions	√			
Co-morbidity	√			
ASIA	√		√	√
Transfer of MRI Scan*	√			
Voice Recording**	√	√***		√
Employment status	√			
Randomisation		√		
Operation details		√		
Complications		√	√	√
Post-operative assessment			√	√
Discharge details				√

*Valid within 12 months of registration

** 25% sample of participants randomly selected at Registration

*** For patients needing a repeated recording only (refer to section 12.4.1)

Table 2: Schedule of Events: Participant completed questionnaires

Events	Pre-surgery questionnaire (Day 0)	Post-surgery follow up (1 day post-surgery)	Post-surgery follow up (6 weeks post-surgery)	Post-surgery postal questionnaires (12, 26, 39 & 52 weeks post-surgery)
NDI	√	√	√	√
PainDETECT	√		√	√
NRS-ULP & NRS-NP	√	√	√	√
EAT-10	√	√	√	√
GETS	√	√	√	√
VHI-10	√	√	√	√
EQ-5D-3L	√	√	√	√
Health Resource Use			√	√

12.3 DATA COLLECTED AT REGISTRATION

At the point of consent and following registration (up to 28 days prior to the planned date of surgery), participants will be asked to complete a Contact Details Form so that the CTRU can post out the follow up participant questionnaires. The form will collect the following information:

- Name
- Postal Address
- Mobile telephone number (for text reminders)/email address (for email reminders) – optional

Prior to registration an Eligibility Checklist will be completed for formal confirmation of eligibility. A Registration Assessment CRF will also be completed by the clinician and will record the information including, but not limited to,

- Participant demographics – gender and ethnicity
- Planned date of surgery
- Height and weight
- Dominant hand of participant
- Details of the pre-operative scan, (type, date of scan, scan results, and confirmation that it has been sent to CTRU)

- Details of previous non-operative interventions for cervical brachialgia
- Pending litigation for the condition
- Current use of analgesics
- Co-morbidities
- Employment status
- Details of voice recording for hoarse voice assessment (see section 12.3.2)

The Registration Assessment CRF will also record the results of the following clinical assessments:

- ASIA Impairment Scale

12.3.1 Hoarse voice assessment

25% of patients will be selected at registration to undergo an additional clinical assessment of hoarse voice. The selected patients will provide a voice recording and other additional data required for blinded central expert review using the GRBAS tool (tool described fully in section 14.2). Additional data collected for these participants includes, but is not limited to:

- Date of voice recording
- Whether or not the participant considers their voice to be “normal” on the day of recording
- Where applicable, reasons for not providing a voice recording will be collected

12.4 DATA COLLECTED ON THE DAY OF SURGERY (Day 0):

On the day of surgery but prior to randomisation, participants will complete a questionnaire booklet containing the NDI, EAT-10, GETS, VHI-10, PainDETECT, NRS-NP & NRS-ULP & EQ-5D-3L questionnaires (see section 12.6).

Following surgery the clinician will complete the operation details CRF recording information including, but not limited to:

- Date of admission for surgery
- Date of surgery
- Confirmation of procedure performed
- Name and grade of principal surgeon
- Details of surgical team: (e.g. doctor/nurse/anaesthetist; grade)
- Level of surgery (C3/4; C4/5; C5/6: C6/7; C7/T1)

- Side of approach (left/right)
- Start and finish times of surgery
- Length of incision
- Total blood loss
- Volume of blood transfusion given (if any)
- Use of antibiotic prophylaxis
- Number of sets of x-rays required
- Use of drill and number of drill tips
- Use of a drain
- Intra-operative complications
- Details of randomised surgical procedure

12.4.1 Hoarse voice assessment

For those patients who were randomly selected at registration to undergo an additional clinical assessment of hoarse voice, and who indicated that their voice was not considered to be “normal” at the time of the registration recording, a further voice recording is required to be collected at this time point. Additional data collected at this time point for these participants includes, but is not limited to:

- Date of voice recording
- Whether or not the participant considers their voice to be “normal” on the day of recording
- Where applicable, reasons for not providing a voice recording will be collected

12.5 DATA COLLECTED POST SURGERY:

12.5.1 Day 1 Post-surgery:

At Day 1 post-surgery, information will be collected on the Post-Operative Assessment– Day 1 CRF. This information is including but not limited to:

- Scan details – if performed for clinical reasons post-surgery (type of scan and results)
- Need for further surgery
- Use of analgesics
- Post-surgical complications – graded using the Clavien-Dindo Classification

The results of the following clinical assessments will also be recorded on the Post-Operation CRF – Day 1:

- ASIA Impairment Scale

12.5.2 Six weeks Post-surgery:

At 6 weeks post-surgery, information will be collected on the Week 6 Follow-up Assessment CRF. This information is including but not limited to:

- Details of post-discharge assessments
- Use of analgesics
- Details of voice recording for hoarse voice assessment (see section 12.5.4)
- Assessment of current symptoms (e.g. type and date of scan, scan results, need for further surgery)
- Post-surgical complications – graded using the Clavien-Dindo Classification

The results of the following clinical assessments will also be recorded on the Post-Operation CRF at 6 weeks:

- ASIA Impairment Scale

12.5.3 Re-operation details

Should the trial team become aware that a participant has undergone a further operation to treat their cervical brachialgia within the 52 weeks after their randomised surgery, this must be reported to CTRU on the Re-operation CRF. This data should be collected from the medical notes, and does not require a participant visit.

12.5.4 Hoarse voice assessment at six weeks

Those participants identified at registration to undergo the additional clinical assessment of hoarse voice will also provide a voice recording at six weeks post-surgery. Additional data collected for these participants includes, but is not limited to:

- Date of voice recording
- Whether or not the participant considers that on the day of recording their voice is significantly different to how their voice has been since surgery
- Where applicable, reasons for not providing a voice recording will be collected

12.6 PARTICIPANT COMPLETED QUESTIONNAIRES

Participants will complete a number of health-related quality of life questionnaires. These will be completed on the day of surgery (Day 0 – Pre-randomisation) and again at Day 1 and 6 weeks post-surgery. Participants will be asked to seal the questionnaires in pre-supplied

stamped addressed envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the CTRU.

The participants will also be posted the questionnaires for completion at 12, 26, 39 and 52 weeks post-surgery and will return them to the CTRU using a pre-supplied stamped addressed envelope. A thank you letter will be sent to participants by CTRU upon receipt of a completed questionnaire. Should a completed questionnaire not be received at CTRU by the required time point, the CTRU will send either a reminder letter or a reminder by SMS or email to the participant depending on their preferred method of contact.

The questionnaires to be completed at the above time points are as follows:

- Neck Disability Index (NDI):
- PainDETECT (NB: This questionnaire is not completed at Day 1 post-surgery)
- NRS-NP & NRS-ULP
- Eating Assessment Tool (EAT-10)
- Glasgow & Edinburgh Throat Scale (GETS)
- Voice Handicap Index-10 (VHI-10)
- EQ-5D-3L

In addition participants will complete the following questionnaires in clinic at 6 weeks post-surgery and will also be posted to participants with the quality of life questionnaires at 12, 26, 39 and 52 weeks.

- Health Resource Use Questionnaire

12.7 PREGNANCY

Any suspected or confirmed pregnancies between the date of randomisation to the date of surgery must be reported to the CTRU **within 7 days** of the research site becoming aware. All further protocolised treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

The CTRU will inform the Sponsor of all reported pregnancies.

12.8 DEATH

All deaths must be recorded on the Notification of Death CRF. Data collected will include but not be limited to:

- Date of death
- Cause of death

All deaths occurring between a participant's randomisation day and the last day of follow up (i.e. 52 weeks post-surgery) must be recorded on the Notification of Death CRF. Deaths occurring within 6 weeks post-surgery should be reported to the CTRU **within 24 hours** of the research team becoming aware of the event.

12.9 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last participant's last data item corresponding to the 52 week follow-up time point.

13. SAFETY REPORTING

For the purpose of this surgical trial, the safety reporting terms adverse events and serious adverse events have been translated into complications.

13.1 GENERAL DEFINITIONS

A **complication** is defined as an untoward medical event in a participant, which has a causal relationship to the trial. The trial includes the trial intervention as defined in section 11.2and any further treatment related to the trial intervention (such as treatment of complications caused by the trial intervention and any trial-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 complication (SC)** is defined as a complication which:

- results in death
- is life-threatening[1]
- requires in-patient hospitalisation or prolongation of an 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

An **Unexpected Serious Complication (USC)** is a **serious** complication which is **related** and **unexpected** and will require expedited reporting to enable 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 trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial.)
- **Unexpected:** that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in section 13.2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 13.4 for Responsibilities). 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.

[1] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

13.2 EXPECTED COMPLICATIONS

The following is a list of expected complications related to the administration of any research procedure including pre and post-operative complications associated with either surgical procedure or the use of general anesthetic;

- Worsening myelopathy / radiculopathy
- CSF leak
- Dural tear
- Spinal instability
- Neurological root injury
- Neurological spinal cord injury
- Vertebral artery injury
- Carotid artery injury
- Jugular vein injury
- Post-operative red eye
- Blindness
- Horner's syndrome
- Oesophagus/pharyngeal injury
- Trachea/laryngeal injury
- Injury to the mouth or teeth from intubation or the breathing tube
- Graft extrusion
- Hoarse Voice
- Neck Pain
- Swallowing difficulties
- Wrong level surgery
- Adjacent segment disease
- Drowsiness, confusion or restlessness
- Nausea and/or vomiting
- Respiratory problems
- Anaphylaxis
- Stroke
- Myocardial Infarction
- Cardiac Arrest
- Soft tissue infection
- Urinary tract infection
- Respiratory infection

- Pulmonary Embolism
- Deep Vein Thrombosis
- Post-operation haematoma
- Pressure sores
- Diathermy burn at the surgical site or location of the diathermy plate

13.3 REPORTING OF COMPLICATIONS:

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

13.3.1 Classification of complications:

All post-surgery complications should be graded using the Clavien-Dindo classification scale where appropriate.

13.3.2 Serious Complications (SCs) and Unexpected Serious Complications (USCs) – expedited reporting

All Serious Complications (SCs) and Unexpected Serious Complications (USCs) (see section 13.1) occurring within 6 weeks of the operation are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event. Notifications must be sent to CTRU by fax or email using the SC / USC CRF. Once all resulting queries have been resolved, the CTRU will request the original form is posted to the CTRU and a copy retained at site.

24 hr fax for reporting SC & USCs: 0113 343 7985 or

forvad@leeds.ac.uk

For each SC and USC, 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)

Any follow-up information on SCs and USCs must be faxed or emailed to the CTRU as soon as it is available. Events will be followed up until resolution or a final outcome has been reached. All USCs will be reviewed by the Chief Investigator (CI) and will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the CI in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements.

13.3.3 All other complications – Non-expedited reporting

Information about the incidence and severity of all other complications (this includes all non-serious expected and unexpected complications) which occur from the date of initial treatment until 6 weeks post-surgery will be collected for all participants on the Operative CRF, Post-Operative Assessment Day 1 CRF or Week 6 Follow-up Assessment CRF, as appropriate.

These events will **not** be subject to expedited reporting requirements.

13.3.4 Untoward medical events unrelated to the trial – Not reportable

It is anticipated that there will be minimal additional risks associated with the interventions in this trial. 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 trial procedures (including the intervention and related procedures or trial-specific procedures such as consent and questionnaire completion).

13.4 RESPONSIBILITIES FOR SAFETY REPORTING

Principal Investigator (PI) (i.e. lead trial clinician at each recruiting research site or appropriate clinical individual identified in the APL)

- Checking for complications 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 SCs and USCs up to 6 weeks post-surgery are recorded and initially reported to the CTRU within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.
- To report SCs and USCs to the CTRU in-line with the protocol.
- To report USCs to local committees in line with local arrangements.

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of SCs and USCs (see section 13.3.2).
    - In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of USCs occurring within 6 weeks post-surgery to the REC and Sponsor within required timelines.
- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of SCs and USCs which compromise participant safety.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Terms of Reference, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Terms of Reference, periodic review of unblinded overall safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

13.5 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 TSC and Sponsor.

Expedited reporting of events (as detailed in section 13.3.2) to the REC and Sponsor will be subject to current HRA guidance, CTRU SOPs and Sponsor requirements.

14. ENDPOINTS

14.1 PRIMARY ENDPOINT

The primary outcome measure is the *Neck Disability Index (NDI)* (31) *at 52 weeks post-surgery:*

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 very 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 (31).

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) (32). 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 (33-35).

NDI exhibits excellent test-retest reliability in patients with cervical radiculopathy and has been found to demonstrate adequate responsiveness in this patient population (35). Several large studies including randomised trials studying brachialgia have used NDI to measure outcome (36-39).

Various studies have been conducted to determine the minimally important clinical difference on NDI (34, 40-42). 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 (35, 43).

14.2 SECONDARY ENDPOINTS

Secondary end-points include:

- *Neck Disability Index (NDI) over 52 weeks post-surgery:* The NDI will be assessed at day 0 pre-randomisation, 1 day, and at 6, 12, 26, 39, and 52 weeks post-surgery to assess the change in the score over time (see primary outcome measure above).

- *Numerical Rating Scales for Neck and Upper Limb Pain (NRS-NP and NRS-ULP) over 52 weeks post-surgery.* NRS-NP and NRS-ULP will be assessed at day 0 pre-randomisation, 1 day, and at 6, 12, 26, 39 and 52 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 (44). 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.

- *EAT-10 swallowing screening tool (45):* The EAT-10 tool will be used to assess dysphagia over 52 weeks post-surgery, and will be collected at day 0 pre-randomisation, 1 day, and at 6, 12, 26, 39 and 52 weeks post-surgery. The tool is a patient-reported outcome measure consisting of 10 items, used to document and monitor the severity of dysphagia. Each item is scored from 0 to 4, with 0 indicating “no problem” for that item, and 4 denoting a “severe problem”. The overall score is obtained by summing the scores for each individual item, and can range from 0 to 40 points, with higher scores corresponding to an increasingly severe swallowing problem.

- *Glasgow-Edinburgh Throat Scale (GETS) (46):* The GETS will be used to assess dysphagia over 52 weeks post-surgery, and will be collected at day 0 pre-randomisation, 1 day, and at 6, 12, 26, 39 and 52 weeks post-surgery. The scale is a patient-reported outcome measure consisting of 10 items, used to evaluate the presence and severity of common throat complaints, especially symptoms of globus (the sensation of a lump in the throat). Each item is scored from 0 to 7, with 0 indicating

"no problem" for that item, and 7 denoting a problem that is "unbearable". The overall score is obtained by summing the scores for each individual item, and can range from 0 to 70 points, with higher scores corresponding to an increasingly severe swallowing problem.

- *Voice Handicap Index-10 (VHI-10) (47):* The VHI-10 will be used to assess hoarse voice over 52 weeks post-surgery, and will be collected at day 0 pre-randomisation, 1 day, and at 6, 12, 26, 39 and 52 weeks post-surgery. The scale is a patient-reported outcome measure consisting of 10 items that evaluate the frequency with which an individual experiences each of 10 statements. Each item is scored from 0 to 4, with 0 indicating "never" for that item, and 4 denoting "always". The overall score is obtained by summing the scores for each individual item, and can range from 0 to 40 points, with higher scores corresponding to an increasingly severe vocal handicap.

- *Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS) scale:* The GRBAS will be used to assess hoarse voice at baseline and at 6 weeks post-surgery. Participant voice recordings for a subset of patients will be collected by sites and sent for blinded central expert review. For the recording, participants are asked to perform three vocal exercises; production of sustained vowels, production of six pre-specified sentences, and the production of spontaneous speech in response to interviewer prompt. These tasks are described in more detail in Appendix 1, and are adapted from the exercises used in the CAPE-V assessment, an alternative method of auditory-perceptual evaluation of voice. It has been shown that there is high reliability and consensus between the GRBAS and CAPE-V scales (48) when applied to voice samples comprising of these tasks, with the GRBAS scale being quicker to complete. Patients who are unable to provide at least 20 seconds of spontaneous speech in response to interviewer prompt will be asked to read a standard passage (the 'rainbow' passage in Appendix 1) instead. The central reviewer is required to score the patient from 0 ("normal") to 3 ("severe"), on the five parameters (grade, roughness, breathiness, asthenia, and strain). Higher scores indicate a more pronounced vocal problem for the parameter in question (49).

- *PainDETECT (50):* A diagnostic questionnaire aimed at assessing whether the pain experienced by a patient is neuropathic or nociceptive in nature. It will be collected at day 0 pre-randomisation and at 6, 12, 26, 39 and 52 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 considered to be ambiguous. The 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.

Additionally, burning (dysesthesia) pain is a feature of neuropathic pain but is usually considered to respond poorly to surgery as it reflects nerve root dysfunction rather than compression. The PainDETECT questionnaire has a single descriptive scale question on the presence and severity of burning pain. Data generated by this item will be summarised separately as well as contributing to the overall scores.

- *Extent and severity of spinal cord functional impairment and nerve root function will be assessed using a restricted version of the ASIA score at the registration assessment, and at 1 day and 6 weeks post-surgery:* The ASIA score 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 (51). 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 the FORVAD 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, because these sensory modalities are carried in different parts of the spinal cord.

  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. Sensory and motor scores will also be calculated for the upper limb on the operated side only using the following areas: C4, C5, C6, C7, C8 and T1. Therefore, the maximum scores for each of these assessments will be 12 (six regions for each of the light touch and pinprick sensory scores on the operated side only) and 25 (five upper limb muscles assessed to derive motor score on the operated side only). A lower score is indicative of a greater degree of functional impairment.

- *Incidence of revision surgery over 52 weeks post-surgery:*
  Patients still being symptomatic at 6 weeks post-surgery, identified from history, examination and persistent nerve compression on repeat MRI, may necessitate further revision surgery. The date, reason and type of surgery will be recorded.

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

  Intra-operative complications:
  Complications occurring during the initial trial operative procedure will be recorded.

  Post-operative complications to 6 weeks post-surgery:
  Post-operative complications will be recorded, and reported by their degree of severity using the Clavien-Dindo classification. Surgical site infection would be noted and categorised based on the Centers for Disease Control and Prevention (CDC) classification. Whether surgical washout is needed in addition to antibiotics will also be recorded. Neurological deficit will be assessed with the ASIA score. Any difficulty with swallowing (dysphagia) and hoarse voice will also be assessed using the EAT-10, GETS and VHI-10 questionnaires as well as the central analysis of the voice recordings using the GRBAS assessment. The need for further surgery and the reason (due to persistent symptoms, spinal instability, infection or wrong level surgery will be recorded).

  Conversion between treatment arms will also be recorded.
- *Cost-effectiveness over 52 weeks post-surgery:*
  Endpoints relating to the economic evaluation are described fully in section 16.

15. STATISTICAL CONSIDERATIONS

15.1 SAMPLE SIZE

A total of 252 patients (126 per arm) is required to have 90% power to detect the minimum clinically important difference of 10% in the change in NDI at 52 weeks post–surgery, assuming a between-patient standard deviation of 23 units (local audit data: Selvanathan et al 2015) (10), 2-sided 5% significance level and 10% loss to follow-up.

To note, as the primary analysis of the primary endpoint is on the absolute NDI score at 52 weeks post-surgery with adjustment for baseline NDI, rather than on the change in score at 52 weeks, the power of the trial on this basis has also been determined. The corresponding power for detecting a 10% difference in the absolute NDI score at 52 weeks post-surgery is 97%, assuming a between-patient standard deviation of 18.83 units (10), 2-sided 5% significance level and 10% loss to follow-up.

Due to the multicentre nature of the trial, we acknowledge the possibility of clustering by centre. Since a stratified-by-centre design is employed in which all centres undertake both procedures, accounting for centre clustering in the sample size calculation by multiplying the standard sample size formula with the design effect 1-ICC would result in a sample size reduction and thus a more efficient design (52). Published literature suggests that clustering by surgeon or centre for a range of long-term patient-reported and QoL outcomes is minimal across various types of surgical interventions (52). Therefore accounting for clustering would result in only a small reduction in sample size e.g. for ICC_{centre}=0.01 reported in the literature for patient reported outcomes at 52 weeks (see Cook et al, Table 3) (52), the design effect would be 1-0.01=0.99; this would result in a 1% reduction to the required sample size requiring a total of 250 patients. We therefore anticipate there will be minimal to no clustering for the primary clinical outcome. We chose a conservative approach to the sample size calculation to allow for the possibility of zero clustering for the NDI at 52 weeks. In the case that there is some clustering present, the trial will be slightly overpowered for the primary clinical outcome.

There is also the possibility of clustering by surgeon. However, due to the nature of the clinical endpoint and as each surgeon is expected to undertake very few cases, this is again expected to be minimal. Moreover, as the number of surgeons within each centre is expected to be very small (2-3 surgeons per centre), surgeon clustering is likely to be confounded with centre clustering. As surgeons are expected to be in equipoise and will undertake both trial interventions, there is no need to inflate the sample size as is typically required in an expertise based design (52).

15.2 PLANNED RECRUITMENT RATE

Assuming a patient pool of over 600 patients per year across 15 centres and a consent rate of 40%, it is estimated that our target sample size requirement of 252 patients randomised will be achieved with an overall average recruitment rate of 10-11 patients/centre/year across 10-15 centres over a 23 month randomisation phase (within a 27 month recruitment phase).

15.3 STATISTICAL ANALYSIS

15.3.1 General Considerations

Statistical analysis is the responsibility of the CTRU statistician. A full statistical analysis plan will be finalised and signed off before any data analyses are conducted.

The primary analysis will be on an intention-to-treat (ITT) basis where patients will be analysed according to treatment allocation determined by the randomisation process. A per-protocol population (PP) will also be defined for sensitivity analyses, which will include all eligible randomised participants according to the treatment actually received but will exclude major protocol violations. This population will be defined in agreement with the Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC) members.

15.3.2 Frequency Of Analysis

Statistical monitoring of safety data will be conducted throughout the trial and reported at agreed intervals to the DMEC. No interim efficacy analyses are planned.

15.3.3 Internal Pilot Phase

An internal pilot phase will determine the likelihood of achieving the planned recruitment rate and of opening the required number of actively recruiting centres, and therefore confirming feasibility of trial delivery to the maximum target recruitment within the planned timelines (see section 8.2). Patient safety and compliance will also be assessed. Details of the progression criteria are detailed separately in the “Internal Pilot Phase” document.

15.3.4 Primary Endpoint Analysis

15.3.4.1 Primary Analysis

Primary analysis on the percentage NDI score at 52 weeks post-surgery will be conducted using a multivariable linear regression will model with covariates entered for the minimisation factors (duration of upper limb symptoms and smoking status), baseline NDI and treatment group. The possibility of fitting centre as a random effect will be explored. The effect of

treatment group will be assessed using a likelihood ratio test comparing models with and without this variable. A range of analyses will be conducted to assess the assumption of normality of residuals.

15.3.4.2 Sensitivity analysis

1. A univariable linear regression model will be fitted to the outcome NDI at 52 weeks post-surgery with covariates entered for baseline NDI and treatment group. The effect of treatment group will be assessed using a likelihood ratio test comparing models with and without this variable. Contrasts for PCF compared to ACD at 52 weeks post-surgery will be reported as the difference in means, together with the corresponding 95% confidence intervals and p-values.

2. A further multivariable model will be fitted to the outcome NDI at 52 weeks post-surgery, in which additional pre-specified baseline covariates shown to have an association with NDI at 52 weeks post-surgery will be fitted to the primary analysis model.

15.3.5 Secondary Endpoint Analysis

Multivariable linear repeated measures models, accounting for within-patient correlation, will also be considered for modelling the NDI, PainDETECT, NRS scores, EAT-10, GETS and VHI-10 scores over time (baseline, 1 day, and at 6, 12, 26, 39 and 52 weeks post-surgery, as appropriate for each endpoint), adjusting for covariates as per the primary analysis model. Time, treatment and treatment-by-time interaction will be fitted as fixed effects. Centre, patient and patient-by-time interaction random effects will also be explored.

Descriptive statistics of the secondary endpoints by treatment group and, where appropriate, over time will be provided. Generalised linear models will be used, using either the identity or logistic link function, including the minimisation factors (duration of upper limb symptoms and smoking status), treatment group, and the appropriate baseline measure for the endpoint in consideration as covariates. Centre will be fitted as a random effect. The effect of treatment group will be assessed using a likelihood ratio test comparing models with and without this variable. Contrasts for PCF compared to ACD at 52 weeks post-surgery will be reported as point estimates (mean or proportion), together with corresponding confidence intervals and p-values.

In addition, complications and serious complications, including occurrence of stroke, paralysis or death, will be recorded and summarised by treatment received. Intraoperative blood loss, waiting time, operative duration and the length of HDU/ICU and hospital stay will also be summarised by treatment group. The use of implant for ACD will also be reported.

Crossover between operative arms will also be summarised.

15.3.6 Exploratory Analysis

Further exploratory analyses will be undertaken to examine the effect of the minimally-invasive approach to PCF (PCF variation) on NDI and EQ-5D-3L by adjusting the appropriate analysis model with a further binary variable denoting if a PCF variation was used or not. The same approach will be taken to assess the potential effect of using a plate as part of an ACD procedure (ACD variation).

Additional exploratory analyses will also be undertaken to assess association of pre-operative MRI scan appearances with pre-operative symptoms and response to surgery. A multivariable model will be fitted for predicting response to surgery. Variables to be considered include, but are not limited to, the position, size and severity of nerve root compression. An internal validation method will be employed to assess the predictive capability of the model.

15.3.7 Missing Data

The amount of missing data and reasons why data is missing will be assessed by treatment group, and based on this assessment imputation of missing data may be considered as documented in the statistical analysis plan.

16. ECONOMIC EVALUATION

16.1 QUALITY-OF-LIFE

EQ-5D-3L questionnaire: administered at day 0 pre-randomisation, and then 1 day, 6 weeks, 13 weeks, 26 weeks, 39 weeks and 52 weeks post-surgery. This questionnaire provides a generic measure of health status (www.euroqol.org) where health is characterised on five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression) (53, 54). Each dimension has three levels (no/some/extreme problems), scored from 1 to 3. The resulting health profile obtained from the questionnaire is used to provide a single value for QoL; the recently generated English tariff will be used to obtain this value (55).

16.2 HOSPITAL RESOURCE USE AND COSTS

Implant use: the use of an implant including a cage or plate for ACD and their type will be recorded. Standardised costs for all implants will be used to calculate surgical cost.

Operative duration: The duration of ACD and PCF will be defined as the time in minutes from skin incision to closure.

Length of Hospital Stay: The length of hospital stay (LOS) will be defined as the number of days from the date of hospital admission to the date of hospital discharge after the administered intervention. The number of days in high dependency unit (HDU) or intensive care unit (ICU) will also be recorded.

16.3 PATIENT HEALTH RESOURCE USE AND COSTS

Patient health resource utilisation form: a bespoke questionnaire to be completed by patients to record health care resource use utilised by patients outside hospital, not otherwise collected within the trial. This will include additional consultations, medication, physiotherapy, etc. and will be used to help inform the additional health care and societal costs for each intervention. Patients will also be asked to record the number of days missed from work because of their surgery. This information will help to inform the additional societal costs for each intervention.

16.4 ECONOMIC ANALYSIS PLAN

A full economic analysis plan will be prepared by the trial health economist, and approved as per the statistical analysis plan. Where appropriate, missing resource use or health outcome data will be imputed. Non-parametric bootstrapped 95% confidence intervals will be estimated (10,000 replicates). We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions. Should the data indicate otherwise, we will develop a generalised linear model to deal with problems such as skewness. Total costs will be combined with QALYs to calculate the incremental cost-utility ratio which will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness specified by the National Institute for Health and Care Excellence. A range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis, and multivariate sensitivity analyses will be applied where interaction effects are suspected. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

17. TRIAL MONITORING

Trial supervision will be established according to the principles of GCP and in-line with the NHS Research Governance Framework (RGF). This will include establishment of a core Project Team, Trial Management Group (TMG), an independent Trial Steering Committee (TSC) and independent Data Monitoring and Ethics Committee (DMEC). A Trial Monitoring Plan will be developed based on the trial risk assessment; this may include site monitoring.

17.1 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU or Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. SDV will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

A Trial Monitoring Plan will be developed.

17.2 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

18. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

18.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) and through adherence to CTRU Standard Operating Procedures (SOPs).

18.2 SERIOUS BREACHES

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree-

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research

In the event of doubt or for further information, the Investigator should contact the Senior Trial Coordinator at the CTRU.

18.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

Ethical approval will be sought through the Health Research Authority (HRA). The trial will be submitted to and approved by a REC, the HRA and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

19. CONFIDENTIALITY

All information collected during the course of the main trial will be kept strictly confidential. Information will be held securely on paper at the CTRU. In addition, the CTRU will hold electronic information on all trial participants. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

The CTRU will comply with all aspects of the UK 1998 Data Protection Act. Operationally this will include:

- Explicit written consent from participants to record personal details including name, date of birth, NHS number (UK participants).
- 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 trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Copies of participants consent forms, which will include participants' names, will be collected when a participant is randomised into the trial by the CTRU. In addition participant name and address will be collected for questionnaire posting. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, research sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

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

19.1 ARCHIVING

At the end of the trial, all data held by the CTRU and all trial data will then be securely archived at the University of Leeds in line with the Sponsor's procedures for a minimum of 15 years.

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

20. STATEMENT OF INDEMNITY

As sponsor, the Leeds Teaching Hospitals NHS Trust does not provide indemnification against claims arising from non-negligent harm.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical study. Therefore, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements under this duty of care.

21. TRIAL ORGANISATIONAL STRUCTURE

Research sites will liaise with the CTRU for advice and support on trial set-up and operation, and submission of trial data. In turn, the CTRU will be responsible for data chasing.

21.1 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 trial. The CI is responsible for the design management and reporting of the study.

Trial Sponsor – Leeds Teaching Hospitals NHS Trust: The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with the NHS Research Governance Framework (RGF), relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and relevant GCP standards and the RGF including randomisation design and service, database development and provision, protocol development, CRF design, trial design, SDV, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and Health

Research Authority (HRA) submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses**.**

21.2 OVERSIGHT / TRIAL MONITORING GROUPS

21.2.1 Trial Management Group (TMG):

The TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the HRA, UK REC and supporting applications for Site Specific Assessments (SSAs)
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of complications
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

21.2.2 Trial Steering Committee (TSC):

The independent TSC will provide overall supervision of the trial (ensuring regular reports to the NIHR HTA Programme), in particular trial progress, adherence to the protocol and consideration of new information. It will include an Independent Chair, not less than two other independent members and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

21.2.3 Data Monitoring and Ethics Committee (DMEC):

The independent DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. Detailed un-blinded reports by treatment group will be prepared by the CTRU for the DMEC at approximately yearly intervals. The DMEC will be provided with detailed un-blinded reports containing the information agreed in conjunction with

the TSC and DMEC. Trial progress will be closely monitored by the independent DMEC, who will report to the TSC.

22. PUBLICATION POLICY

22.1 AUTHORSHIP AND ACKNOWLEDGEMENT

The trial 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 trial 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 trial, 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, other grant co-applicants, the trial management team, the top 5 recruiting Principal Investigators and the top recruiter (not a PI) will be named as authors in any publication. The remaining collaborators (all other PIs, the TSC/DMEC and other recruiters) will be acknowledged in the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the HTA programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the HTA website.

The CTRU is obliged to provide NIHR HTA with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to NIHR HTA at least 28 days prior to submission for publication.

23. Appendix 1- Hoarse Voice Assessment Script

For participants randomly selected at registration to provide voice recordings, the attending trial team will collect a voice recording, at the timepoints outlined in section 11. The trial team will ask the participant to complete the following tasks:

1. **Sustained Vowel Sounds**
   Ask the participant to make the following vowel sounds for 3 to 5 seconds
   - /a/ - pronounced ‘aaah’
   - /i/ - pronounced ‘eee’

2. **Sentence Production**
   Ask the participant to read the following sentences, which can be found on the flashcards located in the investigator site file
   - The blue spot is on the key again
   - How hard did he hit him?
   - We were away a year ago
   - We eat eggs every Easter
   - My mama makes lemon muffins
   - Peter will keep at the peak

3. **Spontaneous Speech**

   This section requires the participant to give 20 to 30 seconds of free flowing speech. To facilitate this, the below question should be asked:

   - Tell me about your journey here today

Optional speech collection

If the researcher is unable to gain 20-30 seconds of speech from the participant in the spontaneous speech section, a scripted passage may be read by the participant as an alternative. The passage used will be ‘The Rainbow Passage’. The script is as follows:

“When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colours. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow.”

Further information regarding performing voice recordings will be provided in the relevant SSOP in the ISF.

24. Appendix 2 – Interview Sub-study

A qualitative sub-study to capture learning from the FORVAD study to inform future studies in cervical brachialgia and neurosurgery.

24.1 Background

Qualitative research, in the form of embedded process evaluations, is now relatively common in trials of behavioural interventions (56) where it can improve recruitment and conduct, contextualise findings and contribute to effective scale-up and impact (57). It also offers additional opportunities to add value beyond the specific trial questions; by enabling broader questions about health and healthcare, such as the experience of health conditions, to be addressed (57). However, it has been more rarely used in drug (5%) surgical (4%) or device (5%) trials (56). This is despite increasing recognition that very few health interventions are truly “simple” (58) particularly in their implementation, and that a failure to recognise complexity may result in inadequate attention to the diverse factors that may impact on the effectiveness of an intervention (for example concomitant interventions, the skill of the person delivering the intervention and the context in which it is delivered (59)).

There is a rich body of qualitative work that considers factors influencing trial recruitment. Patient preference has often been perceived to be a key limiting factor, however qualitative research has demonstrated that preferences may be based on misconceptions and that having an opportunity to explore preferences may reveal a more nuanced view and ultimately willingness to participate (60). Trust in the trial and the associated health professionals are important factors and patients are also strongly motivated by altruism, seeing trial participation as a way to achieve something positive from an otherwise difficult situation (61, 62). However altruism has limits and patients carefully weigh up the pros and cons of participation (61, 62). Clinicians also play an important part in recruitment, either deliberately or inadvertently revealing their own equivocality regarding equipoise, and sometimes struggling to reconcile their research and clinical roles (63, 62). In addition to issues around equipoise, undertaking pragmatic RCTs in surgery may be challenging because of unfamiliarity with pragmatic study designs, a lack of understanding about the value of randomisation in minimising bias and aspects of surgical culture and training that are not supportive of RCTs (64).

The overall aim of this work is to capture learning from the FORVAD study to inform future studies in cervical brachialgia and neurosurgery more broadly. Relatively few RCTs have been conducted in this field and it is important that lessons are learned to increase the chances that future trials in this area can be successfully conducted.

We will examine clinicians' willingness to participate in and recruit to the FORVAD trial and their views about the two treatments. We will discuss with them any difficulties staff experienced running the trial, for example with data collection, the timing of consent, how and who approaches patients. Understanding these issues will help us better understand the results of the FORVAD trial, and identify improvements we can make to the trial design.

Aims

Specifically, this qualitative work aims to:

1. Understand the reasons why the FORVAD study was unable to recruit to target.
2. Identify aspects of trial design and conduct that could be improved in a future RCT of surgical interventions to address cervical brachialgia.
3. Identify and understand any wider issues that may need to be addressed in future randomised controlled trials in neurosurgery.
4. Identify research priorities in cervical brachialgia.

24.2 Method

Design: Semi structured interviews

Interviews with a sample of eligible patients will explore patients' perspectives of treatment, their understanding of the two treatments, and experiences of trial participation.

Interviews with clinical staff will explore their views about the trial, treatments for cervical brachialgia, clinical equipoise, and for participating sites, their experiences of trial participation.

24.3 Sample

Interviews (telephone/video-conference) will be conducted with health professionals and patients from three groups of sites:

1. Sites that successfully randomised one or more patients (n=5)

2. Sites which opened to recruitment but did not randomise any patients (n=6 – health professional interviews only)

3. Sites that initially expressed an interest in participation but did not open to recruitment (n=5 – health professional interviews only)

In sites in groups 1 and 2, a purposive sample drawn from a) site PI b) other participating surgeons c) research nurses and/or other staff involved in the trial will be recruited.

Interviews will explore trial set up, the patient pathway (trial and clinical) and perceptions and experiences of the trial and of trial interventions.

In sites in group 3, the person originally contacted regarding site participation will be approached, a sample of other surgeons, and any other relevant staff involved in the feasibility and set-up process.

It is anticipated that approximately 30 interviews will be conducted to achieve both spread (a range of sites and health professionals) and depth (an understanding of the circumstances at each site). In addition approximately 10-12 patient interviews will be conducted with recruited patients (group 1 sites only) to understand patients' experiences of cervical brachialgia, the study interventions, and to identify any areas for improvement in the patient pathway for a future trial in this area.

24.4 Sample identification and consent process for patients

Patients will be approached by letter by the CTRU team with information about the sub-study and inviting them to return an Expression of Interest (EoI) form if they are interested in participating in an interview. If patients prefer they can contact the University of Leeds research team direct by email using the contact details provided in the participant information sheet. One reminder will be sent, two weeks after the initial approach.

Following receipt of the EoI or email contact, a member of the FORVAD research team will contact the patient to discuss the study in more detail.

Verbal consent will be taken and recorded at the start of the interview using the verbal consent script.

24.5 Sample identification and consent process for staff

All staff involved in the recruitment process, or in the delivery of treatment for cervical brachialgia, at each trial site will be invited to express an interest in participation (local PI, recruiters, local clinical staff). The local Principal Investigator, or for sites which did not open to recruitment, the person at site who had acted as contact for the study, will be asked to distribute participant information sheets to potential participants. Staff members whose contact details are already held by CTRU staff for the purposes of trial communication will also be sent a participant information sheet direct. A reminder will be sent 2 weeks after the first invitation. Staff will be asked to approach the University of Leeds research team direct by email using the contact details provided in the participant information sheet. Snowball sampling (i.e. interviewees mentioning additional staff members likely to be able to contribute useful information on the sub-study topics) will also be used to identify further potential participants at sites.

A purposive sample, chosen to provide variety in terms of geography, site success with recruitment and clinical role of participants will be drawn from those expressing an interest in participating.

24.6 Interview procedure for patients and staff

Interviews will be conducted either by an experienced qualitative researcher, or by a member of the Leeds Teaching Hospitals NHS Trust clinical team under the supervision of an experienced qualitative researcher. At the start of the interview, the researcher will check that the interviewee has read and understood the information sheet, including in relation to the verbal consent process and will answer any remaining questions. If the interviewee is happy to continue, verbal consent will then be taken. A topic guide will be used – this has been developed based on our own and other previous research (63, 62, 65), our theoretical framework (66), and initial conversations with members of the trial team. Interviews will be semi-structured and flexible to accommodate unanticipated areas and the circumstances of the particular interviewee.

24.7 Data analysis

Interviews will be, with consent, audio-recorded, transcribed verbatim and edited to ensure anonymity of respondent. Files will be encrypted before transfer for transcription - a data protection agreement is in place between University of Leeds and the transcription company (Typing Works). The analysis of barriers and enablers to trial set up, recruitment and conduct will be informed by Normalisation Process Theory (66) which has been widely used in trial process evaluations (http://www.normalizationprocess.org/how-do-you-use-npt/trials/) (62). Data will be managed using NVivo software (QSR International). The analysis will be theoretically-informed by Normalization Process Theory and conducted according to the standard procedures of rigorous qualitative analysis (67) including open and focused coding, constant comparison, memoing (68), deviant case analysis (69) and mapping (70). A proportion of data will be analysed collectively in ‘data clinics’ where the research team share and exchange interpretations of key issues emerging from the data.

24.8 Outputs

- An understanding of barriers to participation and recruitment in FORVAD

- Identification of aspects of the trial design that have hindered recruitment

- Identification of possible solutions to recruitment difficulties for future trials in cervical brachialgia.

24.9 Confidentiality

We will be mindful of protecting participant confidentiality at all times. All audio recordings of interviews with patients and staff will be stored on the University of Leeds secure drives and accessed only by researchers involved in data analysis. Following transcription, all the personal data in the transcripts will be removed and/ or anonymised so the participants' identity will be protected. This may include details of events and places which could identify an individual. The participants will then be referred to by a pseudonym which will bear no resemblance to their identity, hospital number, DOB or similar. Any direct quotes used in publications of the results will not identify individuals. This is explained in the participant information sheet.. The audio recordings will be retained until after analysis is completed and will then be destroyed.

It is envisaged that most files will be virtual - any paper documents (e.g. consent forms, demographic questionnaires etc.) and any information about the participant will be kept in a locked cabinet at the University of Leeds. All electronic information will be stored on the University of Leeds' computers which are password protected. The file in which codes are linked to patients' names will only be stored on a password protected computer on a secure network.

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