




# BMJ Open Finnish Trial on Practices of Anterior Cervical Decompression and Fusion (FACADE): a protocol for a prospective randomised non-inferiority trial comparing outpatient versus inpatient care

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## ABSTRACT

**Introduction** Although a great majority of patients with cervical radiculopathy syndrome can successfully be treated non-operatively, a considerable proportion experience persistent symptoms, severe enough to require neurosurgical intervention. During the past decade, cervical spine procedures have increasingly been performed on an outpatient basis and retrospective database analyses have shown this to be feasible and safe. However, there are no randomised controlled studies comparing outpatient care with inpatient care, particularly with emphasis on the patients' perception of symptom relief and their ability to return to normal daily activities and work.

**Methods and analysis** This is a prospective, randomised, controlled, parallel group non-inferiority trial comparing the traditional hospital surveillance (inpatient, patients staying in the hospital for 1–3 nights after surgery) with outpatient care (discharge on the day of the surgery, usually within 6–8 hours after procedure) in patients who have undergone anterior cervical decompression and fusion procedure. To determine whether early discharge (outpatient care) is non-inferior to inpatient care, we will randomise 104 patients to these two groups and follow them for 6 months using the Neck Disability Index (NDI) as the primary outcome. We expect that early discharge is not significantly worse than the current care in terms of change in NDI. Non-inferiority will be declared if the mean improvement for outpatient care is no worse than the mean improvement for inpatient care, by a margin of 17.3%. We hypothesise that a shorter hospital stay results in more rapid return to normal daily activities, shorter duration of sick leave and decreased secondary costs to healthcare system. Secondary outcomes in our study are arm pain and neck pain using the Numeric Rating Scale, operative success (Odom's criteria), patient's satisfaction to treatment, general quality of life (EQ-5D-5L), Work Ability Score, sickness absence days, return to previous leisure activities and complications.

## Strengths and limitations of this study

- Efficacy design: Strict eligibility criteria.
- Special emphasis on the patients' perceptions of early recovery and their self-perceived ability to return to normal daily activities and work.
- Patient-partnership concerning the design of the study, the informational material and the burden of the trial from the patient's perspective.
- Strict eligibility criteria possibly limit the generalisability of the findings.
- Participants' awareness of the group assignment (lack of blinding) increases the risk of performance bias.

**Ethics and dissemination** The study was approved by the institutional review board of the Helsinki and Uusimaa Hospital District on 6 June 2019 (1540/2019) and duly registered at ClinicalTrials.gov. We will disseminate the findings of this study through peer-reviewed publications and conference presentations.

**Trial registration number** NCT03979443.

## INTRODUCTION

Cervical radiculopathy syndrome (CRS) or radiating arm pain caused by cervical nerve root irritation is a common complaint in otherwise healthy working-aged population with an annual incidence of approximately 0.8 per 1000 inhabitants.<sup>1</sup> Conservative treatment is a viable alternative for the majority of patients with CRS, as their symptoms are periodic and improve with time. However, a considerable proportion of patients with CRS experience persisting symptoms severe enough to justify neurosurgical intervention. Anterior cervical decompression and fusion

(ACDF) operation, first described in 1950s by Cloward<sup>2</sup> and Smith-Robinson,<sup>3</sup> has become the gold standard surgery for CRS.<sup>4 5</sup> Originally, the ACDF procedure comprised of decompressing the nerve root followed by replacing the intervertebral disc by an autologous bone graft harvested from iliac crest to fuse the two adjacent vertebral bodies together. After the introduction of PEEK (Poly-Ethane-Ethene-Ketone) and titanium cages, autologous bone grafts are rarely used anymore to avoid morbidity related to the donor site. With the advent of minimally invasive surgical techniques, anterior cervical fusions can now be achieved with reduced tissue trauma, pain and blood loss.

In most countries, the contemporary postoperative clinical practice after ADCF is to keep the patients under surveillance overnight for immediate postoperative complications, typically cervical swelling, neck haematoma and postoperative bleeding in the epidural space. However, a number of recent retrospective database analyses suggest that successful outpatient anterior cervical fusions can be done without an increased risk of complications.<sup>6-8</sup> The surge of outpatient spine surgery, particularly in the USA, is also evident in the recent US-based clinical practice guidelines that advocate early discharge over inpatient care.<sup>9</sup>

To date, no randomised trial has compared outpatient with inpatient care in patients who have undergone ACDF, particularly with a special emphasis on the patients' immediate perceptions of the care given and their self-perceived ability to return to normal daily activities and work. We will conduct a pragmatic, randomised, non-inferiority trial comparing the traditional hospital surveillance (inpatient) with outpatient care (same day discharge, within 6–8 hours after procedure) for patients undergoing ACDF procedure. Non-inferiority of the new treatment (outpatient care) with respect to the reference treatment (inpatient care) is of interest on the premise that the new treatment has some other advantages, such as greater availability, faster recovery, reduced cost, less disabling, fewer adverse events (harms) or greater ease of administration.<sup>10</sup> We hypothesise that with the current technique of performing ACDF, the outcome of patients in the outpatient care group is not worse than in the conventional postoperative strategy (inpatient care), exceeding the non-inferiority margin and with no significantly increased risk of harms. We further hypothesise that patients treated on an outpatient basis would perceive themselves to be less disabled, subsequently encouraging them to return more quickly to their normal daily activities and work. This will be assessed as our secondary objective.

## MATERIALS AND METHODS

### Overview of study design

We will start the FACADE as a single centre prospective randomised non-inferiority study with the primary objective to compare the traditional strategy of keeping

patients under hospital surveillance overnight (inpatient group) to a strategy of early discharge (6–8 hours after procedure, outpatient group) in patients having undergone ACDF procedure. We are planning to expand the FACADE to two or three other university hospital centres in Finland if our recruitment is too slow. We hypothesise that ACDF performed with current techniques will have comparable outcomes and no increased harms in the early discharge arm versus the conventional postoperative arm. Additionally, we hypothesise that patients treated on outpatient basis would perceive themselves as less disabled, subsequently encouraging them to return more quickly to their normal daily activities and work. This will be assessed as the secondary outcome.

### Participant selection and recruiting process

We will screen all patients suffering from radiating arm pain referred to the department of neurosurgery at Helsinki University hospital for trial eligibility by the FACADE investigators. We will carry a standard clinical examination and MRI examination of the cervical spine. Patients with clinical and imaging findings consistent with a diagnosis of CRS and willing to undergo ACDF operation after being fully informed of the trial protocol and the benefits and potential harms of the surgery will be evaluated for eligibility.

### Inclusion criteria

1. CRS unresponsive to non-operative treatment for at least 6 weeks or with severe progressive signs and symptoms of nerve root compression during conservative treatment of shorter duration.
2. CRS is defined as pain, paresis or paresthesia in the corresponding nerve root distribution areas of C5, C6, C7 or C8.
3. Nerve root stenosis determined by MRI at treatment level correlating to CRS/symptoms.
4. Neck Disability Index (NDI) score  $\geq 30$  out of 100.
5. Age between 18 and 62 years.
6. No previous cervical operations.
7. Currently employed.
8. No comorbidities causing a need for a sick leave.
9. Provision of informed consent from the participant.
10. No contraindication for randomisation in postoperative check (see exclusion criterias #8 and #10).

### Exclusion criteria

1. MRI finding inconsistent with patient's symptoms.
2. Diagnosed osteoporosis or permanent use of oral corticosteroids.
3. ACDF operation requiring plate or cage fixation with screws.
4. Active malignancy.
5. American Society of Anesthesiologists Physical Status Classification system (ASA) 4 and 5 patients (seriously ill patients).
6. Pregnancy.
7. Abundant use of alcohol, drugs or narcotics.

8. No possibility to be accompanied by an adult person over the first postoperative night after the surgery.
9. Insufficient Finnish language skills.
10. Distance to the closest hospital emergency more than 60 min.

### Informed consent

At the first appointment, we will provide the patients with detailed written and oral information of the trial and ask patients to sign a consent form. We will ensure that patients understand that the surgical procedure and the ensuing follow-up will be identical irrespective of study group allocation, and that the randomisation only occurs after the surgery. We will also inform the participants that participation in the study is entirely voluntary and any decision they make will not influence any future care. Participants will also be informed of their right to withdraw from the trial whenever they desire without the need to supply any reason for such decision, and in such cases their data acquired prior to withdrawal will be maintained in the study database and included in analysis to avoid bias. Patients who are eligible for the trial, but are not willing to undergo randomisation, will be asked to be included in a simultaneous, pragmatic follow-up cohort.

### Baseline assessment

Our baseline assessment includes documentation of the following characteristics: gender, birth date, education, current employment status, hand dominance, time from the onset of symptoms and recreational habits. We will also ask the participants to assess their physical workload (physically hard/demanding or not), their general health and usage of pain medication. Finally, we will also document any prior conservative treatment (table 1).

### ACDF operation and anaesthesia

A standard anaesthetic procedure will be used. Every patient will be given preoperatively 10 mg diazepam, 1000 mg paracetamol and 90 mg etoricoxib. During the operation, anaesthesia is maintained with propofol infusion with standard amount of fentanyl and rocuron.

FACADE neurosurgeons will carry out a standard ACDF operation as described previously.<sup>4</sup> All FACADE neurosurgeons are members of the Finnish Neurosurgeons Association and have successfully completed at least 100 ACDF operations over the past 5-year period. Interbody fusion is performed with a Poly-Ethane-Ethene-Ketone (PEEK) cage (Cespage, Easculap, BBrauns, Germany) and a confirmatory X-ray will be acquired at the end of the operation for ensuring the correct positioning of the cage. We will instruct the patients not to wear any type of collar postoperatively.

### Randomisation and concealment

After the surgery, we will take all patients to the recovery room for 2–3 hours for an immediate postoperative observation. When we have confirmed that the patients are fully conscious and cooperative, immediate postoperative complications are ruled out using a postoperative

**Table 1** Baseline characteristics

	Outpatient	Inpatient
Age (years), mean (SD)		
Gender (female/male), n (%)		
Dominant hand affected, n (%)		
Work Ability Score (WAS)		
Physically demanding job, n (%)		
Ability to work normally irrespective of the symptoms? n (%)		
Participation in leisure time activities irrespective of the symptoms? n (%)		
Duration of symptoms (days), mean (SD)		
Sick leave duration (days)		
Prior treatments (Physiotherapy) n (%)		
Non-steroidal anti-inflammatory drugs (NSAID) pain medication, n (%)		
Opioid pain medication, n (%)		
Neuropathic pain medication, n (%)		
Euroqol health related quality of life assesment instrument (EQ-5D-5L), mean (SD)		
Neck Disability Index (NDI) scores (0–100 NDI), mean (SD)		
Neck pain at rest (0–10 NRS), mean (SD)		
Arm pain at rest (0–10 NRS), mean (SD)		
NRS, Numeric Rating Scale .		

checklist, and patients' final eligibility is confirmed. A member of the FACADE study group then carries out randomisation. The randomisation is a built-in property in the online electronic case report form (eCRF) system used in the trial. To minimise the risk of predicting the treatment assignment of the next eligible patient (to ensure concealment), we will perform randomisation with variable block size (block size known only to the statistician with no involvement in the clinical care of the participants in the trial).

### Intervention

#### Outpatient (OutP) group

A ward nurse will evaluate all patients allocated to the outpatient group approximately 6–8 hours after surgery using a standardised FACADE discharge checklist. If the patient fulfils all discharge criteria, he/she will be instructed on how to deal with any concerns and will be discharged. At discharge, we will document the time elapsed from operation and provide the patients with prescriptions to manage postoperative pain and an absence from work medical certificate for the first postoperative week.

#### Inpatient (InP) group

Patients allocated to inpatient care will be kept overnight. A neurosurgeon on duty will assess the 'readiness' of the patient to be discharged using the FACADE discharge checklist. Identical to OutP group, at discharge we will document the time elapsed from operation and provide the patients with prescriptions

**Table 2** The follow-up assessments and data collection timetable

Assessment	BL	SG	1 wk	2 wk	3 wk	1 mo	3 mo	6 mo
Informed consent	X							
Baseline form	X							
MRI	X							(X)
Randomisation		X						
Adverse effects		X	X	(X)	(X)	X	X	X
WAS	X		X	(X)	(X)	X	X	X
Return to work			X	(X)	(X)	X	X	X
Return to previous activities			X	(X)	(X)	X	X	X
ODOM			X	(X)	(X)	X	X	X
Patients satisfaction to the treatment								X
Health resource utilisation			X	(X)	(X)	X	X	X
Clinical examination	X					(X)		(X)
NDI	X					X	X	X
NRS-AP	X		X	(X)	(X)	X	X	X
NRS-NP	X		X	(X)	(X)	X	X	X
EQ-5D-5L	X							X

(X) if required.

BL, baseline; mo, month postoperatively; NDI, Neck Disability Index; NRS-AP, Numeric Rating Scale Arm Pain; NRS-NP, Numeric Rating Scale Neck Pain; ODOM, Operative success; SG, surgery; WAS, Work Ability Score; wk, week postoperatively.

for postoperative pain management and an absence from work medical certificate for the first postoperative week.

### Compliance to treatment allocation and possible crossover

If a patient allocated to OutP group does not consider herself/himself fit enough to be discharged or will not pass the discharge checklist (eg, due to severe nausea, neck swelling indicating a possible postoperative haematoma, insufficient relief of radiating upper extremity pain, severe neck pain, severe difficulties to swallow, a new paraesthesia or paresis on upper extremity or a new postoperative dysphonia), we will keep her/him at the ward for as long as deemed necessary. We will consider these patients crossovers.

### Primary outcome measure

#### Neck Disability Index

Our primary outcome measure is the NDI (scale 0–100, with higher scores indicating worse outcomes and more symptoms), a validated, neck-specific, patient-reported measure of pain-related dysfunction<sup>11 12</sup> We will use a validated Finnish version of the NDI.<sup>13</sup> The primary assessment time point is 6 months. We will also query the NDI at 1 and 3 months postoperatively, but these data are only intended to illustrate the trajectory of the treatment responses (table 2). We will consider 17.3% improvement from the baseline value as the minimal important difference (MID) for NDI.<sup>14</sup>

### Secondary outcome measures

#### Neck and arm pain

We will ask the patients to estimate the intensity of their neck pain (NRS-NP) and arm pain (NRS-AP) using a standard internet-based Numeric Rating Scale (eNRS)<sup>15</sup> at baseline, and at 1 week, 1 month and 6 months after the surgery (table 2). We will use an 11-unit NRS scale ranging from 0 (no pain) to 10 (extreme pain). We will consider two points as the MID.<sup>15</sup>

#### Return to previous leisure activities

Before the operation, each patient will be asked to name the most important daily leisure activity they are not able to perform because of the disease. At each follow-up time point (table 2), participants will be asked to respond to the following question: ‘Have you been able to return to your leisure activity?’ (‘yes’ or ‘no’).

#### The single item Work Ability Score (WAS)

Patients will assess their ability to work according to single item<sup>16</sup> WAS preoperatively/at baseline, at discharge after surgery, and 1 week, 1 month and 6 months after the surgery. The single-item WAS is an 11-point NRS in which a patient will assess his or her current work ability compared with the lifetime best, with a possible score of 0 (‘completely unable to work’) to 10 (‘work ability at its best’).

#### The duration of sick leave

We will record the duration of sick leave, that is, the number of sickness absence days both before and after

the operation. The number of sickness absence days will be treated as a continuous variable.

### Other (ancillary) outcome measures

#### EQ-5D-5L

EQ-5D-5L is a standardised health-related quality of life instrument for assessing a patient's general health and treatment outcome<sup>17</sup> and details a patient's self-assessed health profile. The scores can be converted into quality-adjusted life years (QALYs). An improvement of 0.24 QALY will be considered clinically relevant.<sup>14</sup>

#### Patient satisfaction

We will elicit patients' global assessment of satisfaction to the treatment at 6 months after operation with this question: 'If you were to choose again, would you choose an operative treatment?' ('yes' or 'no').

#### Operative success

Operative success will be assessed at each follow-up time point (table 2) by the modified Odom's criteria,<sup>18</sup> in which the patient subjectively rates the perception of operative success from poor to excellent.<sup>19</sup> We will consider the first and second categories ('excellent' and 'good') as a successful outcome of the operation and, conversely, last two categories ('fair' and 'poor') as an unsuccessful outcome.

#### Complications and adverse effects

Complications directly related to the interventions will be registered. Postoperative dysphonia and odynophagia will be assessed with 0 to 10 numerical rating scales NRS-DP (NRS-dysphonia) and NRS-OP (NRS-odynophagia) at each postoperative time point.<sup>20 21</sup> NRS will be assessed on an 11-unit scale ranging from 0 (no dysphonia/odynophagia) to 10 (extreme dysphonia/odynophagia).

The participants will also be encouraged to contact the hospital if any adverse effects occur. The patient's contact with the healthcare system will be registered at every follow-up visit. Potential adverse effects (AEs) will be categorised as serious adverse effects (SAEs) or minor adverse effects (MAEs). Death, cardiovascular events, deep venous thrombosis, pulmonary embolism, systemic infection, postoperative neck haematoma, postoperative monoplegia or tetraplegia, permanent dysphagia or dysphonia will be categorised as SAEs, and local infection, periodic dysphagia or dysphonia will be categorised as MAEs. The number and severity of complications and AEs will be assessed.

#### Follow-up

The full follow-up process is outlined in table 2. Our primary method for collecting follow-up information is an electronic questionnaire. A link to this questionnaire is sent via email to all patients at all follow-up time points. To assess the participants' ability to return to everyday activities and return to work, we will also contact the participants by phone 1 week after the surgery. Special attention will be paid to patient's self-perception of ability to return to work. If a patient is able to return to work, weekly follow-up will be

terminated. If a patient does not feel able to return to work, the sick leave will be extended and a phone contact is scheduled on the next week. Weekly contacts will be continued for up to 3 weeks, if needed. In case of further need for sick leave beyond 1 month, a patient will be invited to an outpatient follow-up visit. We collect data on healthcare resource utilisation at the 1-month, 3-month and 6-month follow-ups. In addition, we also encourage the patients to contact the FACADE study nurse if they encounter any problems that require medical attention at any time over the course of the follow-up.

#### Adherence and loss to follow-up

To safeguard against potential loss to follow-up, we will exclude individuals likely to pose suboptimal adherence to study follow-up, obtain verified contact information from each consented participant and remind the participants of upcoming follow-up visits. All attempts will be made to make follow-up as convenient as possible for the patients. Participants are not required to visit the outpatient clinic postoperatively. Only in case of suboptimal operative result or any other possible concern related to care, a patient will be offered an opportunity to be assessed at the outpatient clinic. Otherwise, follow-ups will be carried out using phone interviews and/or electronic questionnaires to be filled online. The follow-up schedule will not incur any costs to the participants. We will monitor the adherence to follow-up throughout the trial and send reminders to patients who fail to return follow-up questionnaires.

#### Missing items

We will use multiple imputation by chained equations to handle missing data for those statistical analyses that cannot handle occasional missing values.<sup>22</sup> All variables to be included in the final analyses will be forced in the chained equation imputation model and possibly including auxiliary variables available in the dataset. The imputation algorithm, called fully conditional specification, uses specific univariate model for each variable and, for each specific imputed dataset, iteratively imputes each variable with missing values and uses the imputed values in the imputation of other variables.

#### Sample size

The trial is primarily designed to ascertain whether outpatient care is non-inferior to inpatient care, at 6 months after surgery, with NDI as the primary outcome. Only one primary analysis will be used to assess non-inferiority. The trial is powered to detect an MID in the NDI score between the two study groups. We set the MID for NDI (17.3%) as our margin of non-inferiority  $\Delta$  based on the results by Parker *et al.*<sup>14</sup> At the 6-month time point, non-inferiority can be claimed if the lower limit of the CI (based on difference in means in the NDI) is greater than the MID in the primary comparison. According to the CONSORT (Consolidated Standards of Reporting Trials) statement for non-inferiority and equivalence

trials,<sup>10</sup> secondary outcomes can be managed using either a superiority or equivalence framework. In our trial, all secondary outcomes will be assessed with an equivalence hypothesis, but since our trial is not necessarily powered for these comparisons, and to avoid issues with multiplicity, we consider them exploratory or hypothesis-generating.

The sample size calculation is based on the primary outcome measure, NDI at 6 months after the surgery. The sample size is approximated using the equation (Equation 3.12 in Chow: Sample Size Calculations in Clinical Research, Third Edition CRC Press 2018) for non-inferiority test:

$$n_1 = n_2 \text{ and } n_2 = \frac{(z_{\alpha} + z_{\beta})^2 \sigma^2 (1 + \frac{1}{x})}{(\epsilon - M)^2}$$

Assuming no difference between treatment arms ( $\epsilon = 0$  in NDI score improvements), equal sample sizes ( $x=1$ , the SD 23%), a margin of non-inferiority  $\Delta$  of 17.3%, one-sided 2.5% statistical significance criteria ( $z_{\alpha} = 1.96$ ) and 90% statistical power ( $z_{\beta} = 1.28$ ), we will need 44 patients per study group. Assuming a dropout rate of 15%, the group size increases to 52 patients. Accordingly, we set the recruitment target at 104 patients.

### Statistical analysis

We will follow primarily intention-to-treat (ITT) principle in all our analyses. In the ITT analyses, the participants are included as randomised. Per-protocol and on-treatment analyses will also be used to avoid falsely claiming non-inferiority. Summary statistics will be given as mean (with SD) for continuous variables and as frequencies (with %) for categorical variables. Repeated measures mixed model (RMMM) analysis will be used for all continuous variables (both primary and secondary outcomes) where regression coefficients are allowed to differ between study subjects. Statistical significance is set to two-sided 5% level. The RMMM analysis allows the use of all available observations in the dataset, so the full dataset (dataset without multiple imputation) will be used in the analysis. Logistic regression will be used to assess categorical variables. R statistical software (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>) will be used for analyses.

The number and proportion of individuals eligible for and compliant with each follow-up will be documented. We will also carry out an analysis of the demographic and prognostic characteristics between the individuals who withdrew and those who remained in the study.

### Safety considerations

To safeguard against possible complications related to postoperative haematoma, all patients are required to live within 60-min distance from a surgical emergency unit.

### Data management and sharing

All study data will be stored in an eCRF. On receipt of the data, the FACADE personnel, blinded to the group

allocation, will make a visual check of the data and query all missing, implausible and inconsistent data. Hospital patient records will also be used to collect missing data and in interpreting inconsistent or implausible data. Participant files will be maintained in storage (both in electronic and paper format) at the coordinating centre for a period of 15 years after completion of the study.

Data generated by our research will be made available as soon as possible and will be available on reasonable request. Data access request will be reviewed by FACADE steering group. Requestors will be required to sign a Data Access Agreement.

### Blinded data interpretation

As previously,<sup>23 24</sup> we will interpret the results of the trial according to a blinded data interpretation scheme.<sup>25</sup> In brief, an independent statistician will provide the Writing Committee of the FACADE trial with blinded results from the analyses, with the groups labelled group A and group B. The Writing Committee will then interpret the results until a consensus is reached and agree in writing on all alternative interpretations of the findings. Once a consensus is reached, we will record the minutes of this meeting in a document coined 'statement of interpretation', which is signed by all members of the Writing Committee. Only after reaching this common agreement, the data manager and the independent statistician will break the randomisation code and the correct interpretation is chosen. A manuscript will then be prepared and finalised for the publication of the results. Detailed minutes of blinded data interpretation meetings will be provided as a supplement to the trial manuscript.

### Patient and public involvement

To achieve more patient-friendly design for our trial,<sup>26</sup> we recruited six patient experts from the European Patients' Academy on Therapeutic Innovation (EUPATI Finland, <https://fi.eupati.eu/>). They were asked to review the consent form and the study questionnaires and to pilot the online eCRF before these were submitted to ethical institutional review board. Among piloting online eCRF, these experts were asked to assess the burden of the intervention and time required to participate in the research, which both they estimated to be reasonable. After the FACADE study is completed, we will contemplate together with EUPATI Finland how to share the study results to the public.

### Data Safety and Monitoring Committee

The purpose of the Data Safety and Monitoring Committee (DSMC) is to advise the FACADE investigators regarding the continuing safety of the trial participants. The DSMC is comprised of two clinical experts (neurosurgeons) with prior trial experience and a clinical trial methodologist. All members are independent of the trial investigators and have neither financial nor scientific conflicts of interest with the trial.

## Ethics and dissemination

All patients included in FACADE will sign an ethics board-approved consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. All participating centres must obtain ethics board approval from their institution for the study protocol, the consent form template, the CRFs and any additional protocol amendments. Any protocol amendments will be communicated to the site investigators, the ethics board, trial participants and trial registries as necessary.

Information about study patients will be kept confidential and will be managed in accordance with the following rules: (1) all study-related information is stored securely at the clinical site, (2) all possible study patient information in paper form is stored in locked file cabinets and is accessible only to study personnel, (3) all CRFs are identified only by a coded patient number, (4) all records that contain patient names, or other identifying information, are stored separately from the study records that are identified only by the coded patient number and (5) all local databases are password protected.

## DISCUSSION

The rationale for the FACADE trial includes (1) the growth in popularity of ACDF operations carried out as outpatient procedures over the last decade; (2) a lack of rigorous (RCT) evidence verifying the efficacy and safety of outpatient ACDF surgery; and (3) uncertainty regarding the possible effect of hospitalisation (vs early discharge) on the recovery of patients to previous leisure activity and return to work.

According to the CONSORT statement for non-inferiority trials,<sup>27</sup> a non-inferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable amount. Because proof of exact equivalence is impossible, a pre-stated margin of non-inferiority ( $\Delta$ ) for the treatment effect in a primary patient outcome is defined. Non-inferiority of the new treatment with respect to the reference treatment is of interest on the premise that the new treatment has some other advantage, such as greater availability, reduced cost, less invasiveness, fewer adverse effects (harms) or greater ease of administration. In this FACADE trial, we primarily set out to determine whether the outcome of outpatient group is non-inferior to the current standards of care (overnight stay) at 6 months postoperatively. Given that the hallmark symptom of this disease—and also the primary reason the patients seek for medical attention—is the disability caused by radiating arm pain, we felt that the NDI is the most appropriate primary outcome for our trial. Although one can argue that rapid return to normal daily activities and work would be a better indication that a person has reached a stable health status, such contention may not be entirely accurate. Comprehensive data on sustainable return to work (RTW) show that a variety of personal and social

factors have positive and negative influences on sustainable RTW.<sup>28</sup> Obviously, the social environment and how it interrelates with personal factors like attitudes towards work and self-efficacy play a role alongside the alleviation of neck pain as predictors of RTW.

The appropriateness of the chosen margin of non-inferiority  $\Delta$  is obviously a critical methodological issue regarding the validity of any non-inferiority trial. The CONSORT guidance states that it should be specified and preferably justified on clinical grounds, given that a too large margin of non-inferiority  $\Delta$  will increase the risk of accepting a truly inferior treatment as non-inferior.<sup>27</sup> Given this, it could be argued that we should have picked a value smaller than the MID of the NDI as our margin of non-inferiority  $\Delta$ , but as the MID defines the *minimal* important difference, we consider this decision justified.

Although the safety and particularly the long-term—preferably sustained—success is of indisputable primary importance in any surgery, early discharge might pose advantages that currently remain unaddressed. In essence, while keeping patients hospitalised overnight after surgery might increase immediate postoperative safety, it may come at the risk of overcautiousness, increased perceived disability, and increased morbidity/disease toll. Given the existing evidence—primarily from registry-based studies—that suggests that ACDF surgery can be successfully performed as an outpatient procedure without increased safety concerns, we felt intrigued to test a hypothesis that early discharge encourages patients to return to their daily activities and work earlier than if they are hospitalised overnight. This hypothesis is the other primary study question of our prospective randomised trial.

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