The Netherlands Cervical Kinematics (NECK) Trial

Effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation;

A blinded randomised multicenter study

Spine Intervention Prognostic Study (SIPS) Group

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B. Braun Medical B.V. Aesculap
1 INTRODUCTION

Anterior cervical discectomy (ACD) is the basic surgical treatment of patients with radicular pain caused by cervical disc herniation. In 1958, Cloward, Smith and Robinson first described anterior cervical decompression with the use of autologous iliac crest interbody graft (ACDF) to maintain disc height. As early as 1960, Hirsch debated the necessity of interbody fusion. At present, ACDF is defined as the golden standard for cervical disc herniation although there is no evidence that anterior discectomy without fusion is inferior to ACD. The Cochrane Review even mentions advantages (e.g. costs and return to work). Frequently surgeons perform ACDF to maintain disc height and cervical alignment, and promote bony fusion to prevent instability. However, arthrodesis of a motion segment leads to increased degenerative changes at the adjacent level. One of the rationales of artificial disc implantation is to restore disc height, maintain motion and subsequently prevent accelerated adjacent level disease. The Netherlands Cervical Kinetics (NECK) trial is designed to demonstrate the effectiveness and security of cervical disc prosthesis, focused on adjacent segment degeneration and functional outcome. Anterior cervical discectomy with disc prosthesis (ACDP) will be randomly and blindly compared with ACD and ACDF.

1.1 Background

A cervical radicular syndrome due to disc herniation is a well-known entity with an annual incidence rate of 83 per 100,000. Patients usually present with radicular arm pain and paraesthesia, with or without neck pain. More than 90% of the patients have a favourable outcome with conservative treatment only and surgery is indicated whenever disabling pain persists. Since the introduction of anterior approach of the cervical spine by Cloward, Robinson and Smith, a dispute has started about the best surgical treatment. The purpose of all surgical procedures is removal of the intervertebral disc in order to decompress the nerve root and alleviate radicular pain. However, cervical instability and segmental collapse with recurrent radicular pain has been documented after anterior discectomy. For this reason, most surgeons, internationally, perform anterior discectomy with interbody fusion while most academic surgeons perform a discectomy sec as a result of lack of evidence. Various prospective randomised trials have been performed comparing anterior discectomy with additional interbody fusion. These results suggest that interbody fusion may not be necessary in all cases. However, definite conclusions could not be drawn due to methodological flaws such as small sample size, non-homogenous patient population, undefined randomisation procedures and inconsistent outcome measures.

One of the main drawbacks of arthrodesis of a motion segment is increased load and stress at the levels adjacent to the fusion site. The concept of accelerated adjacent disc degeneration (AADD) is widely discussed. Hillbrand et al. reported a large retrospective study of patients who underwent anterior discectomy with fusion. Symptomatic adjacent level degeneration occurred at a relative constant incidence of 2.9% annually. They predicted that 25.6% of the patients would have new disease at the adjacent level within 10 years after the operation. Goffin et al. showed 92% additional radiological degeneration at the adjacent disc levels at late follow-up after anterior cervical interbody fusion.
Gore evaluated 200 asymptomatic persons radiographically. At 10 years follow-up he showed new or progressive degenerative changes in 100 of the 159 participants (63%) and 15% reported pain. These results suggest that intervertebral disc degeneration is a physiological process, which may be accelerated by interbody fusion. In accordance to these findings, Okada et al. found progression of degenerative findings in 81% of patients in a longitudinal 10-year follow-up, of which 34% were symptomatic.

The main rationale of artificial disc replacement is motion preservation with subsequent prevention of adjacent disc degeneration. Various prospective randomised trials have shown that cervical disc prosthesis is a safe and reliable alternative to cervical fusion. Concerning adjacent disc disease, Robertson et al. documented 1.3% (0.65% per year) symptomatic adjacent level disease in the arthroplasty group versus 13.9% (6.9% per year) in the fusion group at 2 years follow-up. Pimenta et al. showed 0.82% symptomatic adjacent level disease at 3 years follow-up. Mummaneni et al. reported the clinical and radiographic results of 541 patients randomly assigned to arthroplasty and allograft fusion. The arthroplasty group had a significant higher neurological success rate as well as lower rate of revision surgeries. However, radiographic evidence of adjacent level degeneration was not assessed in this study.

Postoperative neck pain is frequently documented after anterior approach of the cervical spine on the short and long term. Whether cervical disc replacement could reduce postoperative neck pain is not known.

In the present study protocol, we will randomly and blindly compare anterior cervical discectomy sec (ACD), with anterior discectomy with fusion (ACDF) and disc prosthesis (ACDP) in 3 treatment groups. We hypothesise a difference in symptomatic adjacent level disease in favour of disc prosthesis and better clinical outcome and self-assessment measured by the Neck Disability Index (NDI). Symptomatic adjacent level disease is defined as development of new symptoms (e.g. neckpain, radiculopathy or myelopathy) referable to a motion segment adjacent to the site of previous anterior surgery. Adjacent level disease (according to Hilibrand’s and Goffin’s criteria) will be used as primary outcome measure and NDI as secondary outcome. As such we will evaluate the clinical appropriateness and superiority of disc prosthesis on one hand, cervical fusion on the other hand and compare this to discectomy without any implant.

1.2 Rational of clinical investigation

This study will investigate whether anterior discectomy with disc prosthesis has a lower incidence of symptomatic adjacent disc degeneration compared to anterior discectomy sec and anterior discectomy with fusion. In addition, the clinical outcome and (cost-) effectiveness will be investigated in the 3 different treatment groups.

1.2.1 Investigational Medical Device

The investigational device is the activ-C Flat artificial cervical disc (B.Braun Aesculap) that is designed to provide a new treatment modality as an alternative to fusion with or without rigid internal fixation. The device is a modular system that is intended to stabilise the spine following discectomy without fusion, thereby restoring the intervertebral height and preserving flexibility at the operative level(s) of the cervical spine. It is indicated for use in treatment of degenerative disc disease at one or two levels of the cervical spine.
from C3-C4 to C7-T1, in skeletally mature patients with accompanying radicular pain. The activ-C Flat cervical disc prosthesis is designed to provide an additional therapeutic option to maintain motion, segment position and spacing while preserving flexibility in the adjacent cervical vertebral levels. The active-C has been widely used in clinical practice with more than 3000 implantations being registered worldwide. Ten selected spine centers in Europe have been continuously monitoring the results since the market launch of activ C.24

The activ-C Flat device is comprised of two flat Cobalt-Chrome -Molybden alloy metal endplate components with spikes on the superior endplate and a keel on the inferior endplate for primary stability. The endplates are Plasmapore® coated to improve bone ingrowth for secondary stability. The implants are available in three heights (5, 6, and 7 mm) and six sizes footprints, ranging from extra small (13 by 16 mm) to extra-extra large (18 by 19 mm).

1.3 Summary of clinical testing

The preliminary data from the ten center experience with the first 89 patients treated with activ-C were published by Suchomel recently.24 Thirtyone patients had a follow-up of 6 months. The mean VAS neckpain improved from 48.7 to 20.3, the mean VAS arm pain improved from 48.8 to 18.2, and the NDI was reduced from 39.5 to 21.6. There were no infections, recurrent laryngeal nerve palsy, or re-operations due to implant failure.
2 DEVICE RISK ANALYSIS AND RISK ASSESSMENT

2.1 General surgical risk assessment
Many of the risks of surgical complications associated with implantation cervical disc prosthesis are expected to be comparable to the risks associated with conventional anterior cervical surgery. The general risks associated with both disc arthroplasty and fusion surgery, as with any surgical or medical procedure, are the potential for infection, blood clots in the veins and lungs, blood loss or haemorrhage, allergic reactions, postoperative pain, complications of anaesthesia, and even death. In addition, the anterior surgical approach in patients with cervical disc herniation may be associated with dysphagia, dysarthria or hoarseness due to vocal cord paralysis.

2.2 Device risk analysis
Specific risks associated with implantation with the activ-C Flat device may be breakage, degradation, displacement or ossification of the device, which will not lead to neurological sequels.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 Null-Hypotheses:
The incidence of symptomatic adjacent disc degeneration after cervical disc arthroplasty is equal to anterior discectomy with or without interbody fusion at 2 years after surgery.

3.2 Primary objective:
To evaluate the incidence of symptomatic adjacent disc degeneration after cervical disc arthroplasty and discectomy with or without fusion at 2 years after surgery.

3.3 Secondary objective:
To evaluate if anterior discectomy with disc arthroplasty is more effective than anterior discectomy with fusion and anterior discectomy without fusion 2 year after surgery.

4 STUDY DESIGN

4.1 Overall design
The study is designed as a multicenter randomised trial with 5 years follow-up, in which patients will be allocated to 3 surgical treatment groups. Patients and research nurse will be kept blinded for 2 years.

Group A: anterior cervical discectomy (ACD or sec)
Group B: anterior cervical discectomy with interbody fusion (ACDF or fusion)
Group C: anterior cervical discectomy with disc prosthesis (ACDP or motion)
4.2 Participating centers

Participation will be requested from all patients with cervical disc herniation who meet the selection criteria in 4.3.1 of the participating hospitals:

- Medical Center Haaglanden, The Hague
  - Bronovo Hospital, The Hague
  - Groene Hart Hospital, Gouda
  - Antoniushove, Leidschendam
  - Vlietland Hospital, Schiedam
  - Reinier de Graaf Hospital, Delft
- University Medical Center Groningen
- Leiden University Medical Center
  - Spaarne Hospital, Hoofddorp-Heemstede
  - Rijnland Hospital, Leiderdorp
  - Diaconessen Hospital, Leiden
- Slotervaart Hospital Amsterdam
- Medical Center Alkmaar
- Maastricht University Medical Center

4.3 Patient selection

Patients will be eligible for study participation if they meet the following in- and exclusion criteria:

4.3.1 Inclusion criteria:

- Age 18-65 years
- Radicular signs and symptoms in one or both arms (i.e., pain, paraesthesia or paresis in a specific nerve root distribution)
- At least 8 weeks prior conservative treatment (i.e., physical therapy, pain medication)
- Radiographic diagnosis of cervical disc herniation and/or osteophyte at 1 level (C3-C4 to C7-T1) in accordance with clinical signs and symptoms
- Ability and willingness to comply with project requirements
- Written informed consent given by the subject or the subject's legally authorised representative

4.3.2 Exclusion criteria:

- Previous cervical surgery (either anterior or posterior)
- No motion of the index level on dynamic studies
- Increased AP translation of the index level on dynamic studies (> 3 mm)
- Involved disc level fused or very narrow (central < 3 mm)
- Severe segmental kyphosis of the involved disc level (> 3 degrees)
- Neck pain only (without radicular symptoms)
- Symptoms and signs of chronic myelopathy
- Infection
- Metabolic and bone diseases (osteoarthritis, severe osteopenia)
- Neoplasma or trauma of the cervical spine
- Spinal anomaly (Klippel Feil, Bechterew, OPLL)
- Severe mental or psychiatric disorder
- Inadequate Dutch language
- Planned (e)migration abroad in the year after inclusion

4.4 Randomisation procedure

Patients will be randomly allocated to ACD, ACDF, or ACDP. Randomisation will take place on the operating room within 6 weeks after the first visit to the research nurse. A randomisation list is prepared for every participating hospital-nurse combination by the biostatistician Ronald Brand (Department of Biostatistics, Leiden University Medical Center). Variable sized blocks of random numbers are formed to ensure equal distribution of the randomisation treatments over hospitals and research nurses. The data manager, who is not involved in the selection and allocation of patients, will prepare coded, sealed envelopes containing the treatment allocation. In the operating room, after induction of anaesthesia, the surgeon will open the envelope and the allocated treatment will be performed. Patients and research nurses will be kept blinded for the allocated treatment for 2 years.

5 DESCRIPTION OF SURGICAL TECHNIQUES

Three techniques are subject of this study:

Group A. All patients will be positioned prone with their neck in neutral position or slightly extended under general anaesthesia. The affected cervical disc level will be verified with fluoroscopy. A small transverse incision will be made either on the right side or the left side depending on the surgeon’s preference. Medial to the carotic sheath, the pre-vertebral space will be opened and the anterior cervical spine will be exposed. Caspar spreader and 2 distraction pins will be placed in the affected segment. A standard anterior discectomy with the aid of loupe magnification or microscope (depending on the surgeon’s preference) will be performed in all cases. The posterior longitudinal ligament will be opened and the nerve root and dura will be decompressed adequately. If required a vacuum drain will be placed and the wound will be closed in layers.

Group B. Once the anterior discectomy has been performed, an interbody cage filled with bone substitute will be placed within the intervertebral space under fluoroscopic guidance. The type of cage depends on the surgeon’s preference and daily practice.

Group C. After the standard anterior discectomy is performed, the implant size (5, 6, or 7 mm) will be determined and the endplates will be prepared for proper fitting of the activ-C Flat prosthesis. The activ-C Flat device will be inserted under slight distraction and fluoroscopic guidance.
Whenever, for surgical-technical reasons, it is not possible to implant a disc prosthesis, an interbody fusion will be performed. Whenever this is impossible as well, only discectomy will be performed. Postoperatively, all patients will be encouraged to mobilise as soon as possible without a collar.

6 VARIABLES TO BE MEASURED

6.1 Demographic data

Of all participating patients the following data will be collected: date of birth, sex, nationality, highest education, profession, smoking habits, previous neck trauma, hobbies, sport, previous neck / arm pain and family history concerning neck and arm pain. Medical history, concomitant medication, weight and length will be collected as well.

6.2 Physical and neurological investigation

A general physical examination (cardiopulmonary, pulse, blood pressure) and neurological examination focused on neck and arm will be performed.

Motor function
Muscle strength of the deltoid (C5), biceps ((C5),C6), brachioradial (C6), triceps (C7), finger extension (C7), finger flexion (C8) and finger spreading ((C8),T1) will be graded by the investigator according to the Medical Research Counsel (MRC) scale:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No movement</td>
</tr>
<tr>
<td>1</td>
<td>Trace of muscle contraction</td>
</tr>
<tr>
<td>2</td>
<td>Active movement without gravity</td>
</tr>
<tr>
<td>3</td>
<td>Active movement against gravity</td>
</tr>
<tr>
<td>4</td>
<td>Active movement against resistance</td>
</tr>
<tr>
<td>5</td>
<td>Normal response</td>
</tr>
</tbody>
</table>

Sensation
Sensation of dermatomes C4 to C8 will be graded by the investigator according to the following categories:
Table 2. Sensory deficit categories

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Hypaesthesia</td>
</tr>
<tr>
<td>Anaesthesia</td>
</tr>
<tr>
<td>Dysaesthesia</td>
</tr>
</tbody>
</table>

**Reflexes**
The muscle tendon reflexes of the biceps ((C5),C6), radialperiost (C6) and triceps (C7) will be documented. Also the Hoffmann-Trömner reflex and the plantar response of the toe will be examined.

**Provocation tests**
Various pain provocation tests of the arm will be examined: foraminal compression test according to Spurling, Valsalva manoeuvre, shoulder abduction relief test and upper limb tension test (Lasegue of the arm).25

6.3 Neck Disability Index (NDI) (secondary outcome measure)
The NDI is a 10-item questionnaire on 3 different aspects: pain intensity, daily work related activities and non-work related activities. Each item is scored from 0 to 5 and the total score ranges from 0 (best score) to 50 (worst score). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology.26-28

6.4 Short-Form 36 (SF-36)
This is a generic health status questionnaire that can easily be filled out at home. The questionnaire consists of 36 items on physical and social status of the patient subdivided in 8 domains; 1) physical functioning, 2) physical restrictions, 3) emotional restrictions, 4) social functioning, 5) somatic pain, 6) general mental health, 7) vitality and 8) general health perception. The questions are scored on a scale of 0 (worst health) to 100 (ideal health). This questionnaire has been used frequently and is validated in surgical studies on spinal column pathology.29 ,30 ,31

6.5 Pain
Pain intensity, measured by McGill pain Questionnaire and Visual Analogue Score (VAS) of arm pain and neck pain, is chosen as secondary outcome measure.
VAS of arm pain. This parameter will measure the experienced pain intensity in the arm during the week before visiting the research nurse. Pain will be assessed on a horizontal 100 mm scale varying from 0 mm (no pain) to 100 mm (worst pain imaginable). Patients do not see the results of earlier assessments and will score the pain experienced at the visit. Reliability, validity and responsiveness of VAS have been shown.³²

VAS of neck pain. Since many patients with radicular arm pain have neck pain as well, we will also measure the intensity of solitary neck pain.

McGill Pain Questionnaire. The McGill Pain score consists of 4 parts: 1) quality and intensity of pain, 2) effects of pain on daily activities, 3) VAS, and 4) distribution and course of pain. The McGill pain score is shown to be highly effective to evaluate the effects of treatment on pain.³³ The Dutch version of McGill pain score will be used in this study.³⁴

6.6 Karasek Job Content Questionnaire

The Job Content Questionnaire is developed by Karasek to measure the on-the-job impact of chronic health problems and/or treatment.³⁵ We will use the Dutch version of the Karasek which has been shown reliability and validity.³⁶

6.7 Hospital Anxiety Depression Scale (HADS)

The HADS is a self-assessment scale which is developed to detect anxiety and depression in patients attending a medical clinical and has been shown reliable and valid.³⁷ The HADS consists of a 7-item depression scale and a 7-item anxiety scale. The score ranges from 0-21 with a high score being indicative for depression/anxiety.

6.8 Perceived recovery

This is a 7-point Likert scale measuring the perceived recovery, varying from 'complete recovery' to ‘worse than ever’. This outcome scale has been used in previous studies and is regarded valid and responsive to change.³⁸ Next to this global self-assessment, a job and hobby specific Likert will be scored. During the intake of the study the patient will be asked to rank their 5 most important functional disabilities in daily life, which they can use in their own evaluation overall and in separate items. Moreover, the expected recovery from both patient, surgeon and research nurse will be evaluated.

6.9 Cost-utility

6.10.1 Utility measures

The EuroQol (EQ-5D) measures five dimensions (mobility, self-care, daily activities, pain/discomfort, anxiety/depression), on a three point scale (no, some, or extreme
problems). For each health state described by the patients, a utility score can be calculated that reflects society’s valuation of that health state. The Dutch tariff for the EQ-5D will be used. Similarly, SF-6D utilities will be calculated from the SF-36 profiles. Whereas the EQ-5D and SF-6D provide society’s valuation for the patients’ health, the patients themselves will also provide their own valuations for their health on visual analogue scales, ranging from 0.0 (as bad as death) to 1.0 (optimal health). VAS values will be converted to utility scales using the power transformation $U = 1-(1-VAS)^{1.61}$.

Both the EQ-5D and the VAS will be reported in questionnaires, filled out at home.

6.10.2 Costs

In a cost-analysis in participating hospitals the direct medical costs will be estimated for the hospital admission (fixed costs per admission, and variable costs per admission day) and for surgery (including personnel and implanted cages and disc prosthesis). Using cost diaries, the patients will register other medical care (including physiotherapy, visits to general practitioners and medical specialists, nursing care and medication) and non-medical costs (including out-of-pocket expenses, domestic help and absenteeism). Each diary will cover three months and the research nurse will go through the diary with the patient on every follow-up visit, throughout the study period of 5 years. Costs will be valued using standard prices, including time and travel costs.

6.10 Re-operation incidence

In general, re-operation is considered as bad outcome and therefore used as an outcome measure. The incidence of re-operation in the 3 groups will be measured.

6.11 Complications

A systematic assessment of complications (including wound infection, deep venous thrombosis, urine tract infection, haematoma, progressive neurological deficit, dysphagia and hoarseness) will be carried out by the surgeon and research nurse. Surgeons will also document perioperative complications like cerebrospinal fluid leakage, vascular injury, nerve root damage, and malposition of the interbody cage or disc prosthesis.

6.12 Perioperative data

Various data of surgery and hospitalisation will be documented on standard Case Record Forms (CRF): left or right sided approach, type and size of implant, duration of surgery, estimated blood loss, operative and postoperative complications, day of mobilization and duration of hospitalisation.
7 CLINICAL INVESTIGATION PROCEDURES

7.1 Intake

Patients are referred by a neurologist with MRI and conventional imaging of the cervical spine. During the first visit to the neurosurgical outpatient clinic, the patient's history and a standard neurological examination will be documented. A dynamic X-ray of the cervical spine will be performed. These examinations are standard and would have been done beyond the study. Conform our selection criteria, the neurosurgeon decides whether a patient is eligible for the NECK trial. The study will be explained to the patient and, in case of a positive reaction, an appointment is made with one of the research nurses. Because the patient needs some time to consider participation, the second visit (first visit to the research nurse) is planned after at least 2 days. After informed consent, the questionnaires, outcome measures and baseline variables are recorded.

As the disc prothesis is subject of the study and not usual care, no disc prothesis will be implanted in patients not participating in the trial.

7.2 Randomisation

Patients will be randomly allocated to ACD, ACDF, or ACDP. Randomisation will take place on the operating room within 6 weeks after the first visit to the research nurse. Patients and research nurse will be kept blinded for the allocated treatment for 2 years.

7.3 Follow-up assessment

Follow-up of all patients will be performed in accordance to the flow chart (Table 4). At 2 weeks, 4 weeks, and 12 weeks after surgery, questionnaires will be sent by mail.
Table 4 Flow chart

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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</thead>
<tbody>
<tr>
<td>Inclusion / exclusion criteria</td>
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<td>Informed consent</td>
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<td>Expected recovery</td>
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<tr>
<td>Basic physical examination</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Re-operation</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
8 RADIOLOGICAL ASSESSMENTS

8.1 Radiography

Anterior/posterior, lateral and flexion/extension x-rays will be performed at each visit. Instability is defined as > 3 mm AP translation during flexion/extension.

8.1.1 Cervical curvature and segmental motion

At intake and each follow-up moment the cervical curvature (angle between the caudal endplate of C2 and the caudal endplate of C7) and the angle between the adjacent vertebrae will be measured in neutral position using Cobb criteria. Dynamic flexion/extension x-ray will be performed to evaluate segmental motion and will be assessed using radiographic analysis software (SpineView).

8.1.2 Adjacent disc degeneration (ADD) (primary outcome measure)

Radiographic degenerative changes at the superior and inferior adjacent levels will be recorded by means of X-ray at intake and each follow-up moment. At 2 and 5 year follow-up both CT and MRI of the cervical spine will be performed. Several criteria have been proposed to evaluate the degree of degeneration at adjacent levels. In this protocol we will evaluate a combination of the grading systems according to Hilibrand and Goffin. Hilibrand used a system based on both plain radiography, MRI and CT. Goffin only evaluated plain radiography and focused on adjacent disc height and anterior osteophyte formation (Table 5). It is of uppermost importance that radiological adjacent level disease is accompanied by concomitant complaints. In accordance with Hilibrand, we will define “symptomatic adjacent level disease” as a combination of radiological and clinical presentation (e.g. neckpain, radiculopathy or myelopathy) but we will evaluate “radiographic adjacent level disease” without symptoms as well.

Table 5. Grading system of ADD according to Hilibrand and Goffin

<table>
<thead>
<tr>
<th>Grade</th>
<th>Disease</th>
<th>X-ray Hilibrand</th>
<th>X-ray Goffin</th>
<th>X-ray Goffin</th>
<th>MRI</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>Normal</td>
<td>Normal (same as adjacent disc)</td>
<td>No anterior osteophyte</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
<td>Narrowing of disc space, no posterior osteophytes</td>
<td>75 – 100 % of normal height</td>
<td>Anterior osteophyte just detectable</td>
<td>Signal change in intervertebral disc</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>&lt; 50% of normal disc height, posterior osteophytes</td>
<td>50 – 75 % of normal height</td>
<td>Clear anterior osteophyte &lt; ¼ of AP diameter of vertebral body</td>
<td>Herniated disc without neural compression</td>
<td>Herniated disc, no nerve root cut-off or spinal cord compression</td>
</tr>
<tr>
<td>IV</td>
<td>Severe</td>
<td>Same as for Grade III</td>
<td>&lt; 50 % of normal height</td>
<td>Large anterior osteophyte &gt; ¼ of AP diameter of vertebral body</td>
<td>Spinal cord compression with or without nerve root compression</td>
<td>Nerve root cut-off with or without spinal cord compression</td>
</tr>
</tbody>
</table>
In addition, we will use a recently developed MRI-based grading system for cervical intervertebral disc degeneration, which has been shown reliable. (Table 6) During the follow-up, a transition from ‘grade 1’ or ‘no degeneration’ to ‘grade 2’ or ‘mild degeneration’ was indicated as an increase in degeneration score of 1 point, a transition from ‘grade 1’ or ‘no degeneration’ to ‘grade 3’ or ‘moderate degeneration’ an increase in degeneration score of 2 points, etc. Looking at both cranial and caudal adjacent levels, the most severely degenerated level determined the increase in degeneration score.

Table 6. MRI-based grading system for cervical intervertebral disc degeneration according to Miyazaki.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nucleus signal intensity</th>
<th>Nucleus structure</th>
<th>Distinction of nucleus and annulus</th>
<th>Disc height</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hyperintense</td>
<td>Homogenous, white</td>
<td>Clear</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Hyperintense</td>
<td>Inhomogenous with horizontal band, white</td>
<td>Clear</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>Intermediate</td>
<td>Inhomogenous, grey to black</td>
<td>Unclear</td>
<td>Normal to decreased</td>
</tr>
<tr>
<td>IV</td>
<td>Hypointense</td>
<td>Inhomogenous, grey to black</td>
<td>Lost</td>
<td>Normal to decreased</td>
</tr>
<tr>
<td>V</td>
<td>Hypointense</td>
<td>Inhomogenous, grey to black</td>
<td>Lost</td>
<td>Collapsed</td>
</tr>
</tbody>
</table>

8.1.3 Displacement or migration of the device (group B and C)

Displacement or migration of the device will be assessed by using a standard lateral radiograph. Only a change of >3 mm will be considered clinically significant due to the margin of error in radiographic determination of displacement distances.

8.1.4 Radiolucency (group B and C)

Radiolucency at the metal bone interface will be assessed as either present or absent by the investigator using a standard lateral radiograph. The presence of radiolucency will be considered clinically significant.

8.1.5 Heterotopic ossification (HO)

Heterotopic ossification is a well-known complication in joint replacement and has also been demonstrated in cervical artificial discs. McAfee proposed a simple classification for HO in lumbar disc replacement which was recently validated. In this study, we will use the classification of McAfee based on lateral X-rays (Table 7).
Table 7. Heterotopic ossification classification according to McAfee

<table>
<thead>
<tr>
<th>Grade</th>
<th>Heterotopic Ossification (HO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No HO</td>
</tr>
<tr>
<td>1</td>
<td>HO present as islands of bone within soft tissue but not influencing segmental motion (bone is not between the planes formed by the two vertebral endplates)</td>
</tr>
<tr>
<td>2</td>
<td>HO present between the two planes formed by the vertebral endplates, but not blocking motion</td>
</tr>
<tr>
<td>3</td>
<td>The range of motion of the vertebral endplates is blocked by the formation of HO on flexion-extension radiographs</td>
</tr>
<tr>
<td>4</td>
<td>HO causing inadvertent bony ankylosis</td>
</tr>
</tbody>
</table>

8.2 MRI / CT / CT Myelogram

MRI, CT or CT myelogram will be performed at the screening visit and after 1 and 5 years to evaluate adjacent disc degeneration. These procedures may also be performed at subsequent visits according to the investigator’s discretion. For MRI, T1/T2 weighted sagittal and axial sequences will be performed at 2 mm slices. For CT, axial images at 2 mm slices will be taken. Contrast media may or may not be given depending on investigator discretion.

9 CLINICAL INVESTIGATION TERMINATION

9.1 Early discontinuation of individual subjects

Subjects will be informed that they are free to withdraw from the project at any time and for any reason, without affecting their subsequent treatment. In addition, a subject may be removed from the project if, in the investigators’ opinion, it is not in the best medical interest of the subject to continue the project. If a subject is withdrawn from the project they will be asked to return to the clinic as soon as possible to perform the assessments for week 104. In addition, the date the subject is withdrawn from the project and the reason for withdrawal will be recorded on the CRF. Subjects who discontinue will not be replaced.

9.2 Early discontinuation of all subjects

If, for any reason, the whole project is discontinued, all subjects ongoing in the project at that time will be asked to return to the clinic as soon as possible to perform the assessments for week 104.
10 ADVERSE EVENTS

10.1 Adverse event

An “adverse event” is defined as “any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the investigational device”. An adverse event can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a device. Adverse events will be followed-up until resolved or stabilised, or until the end of the defined follow-up period (260 weeks), whichever occurs first.

10.2 Serious Adverse Events

A “serious adverse event” is defined as one of the following:

- An event causing the death of the subject
- An event which leads to a serious deterioration in the health of a subject that:
  a) Results in a life-threatening illness or injury
  b) Results in permanent impairment of a body structure or a body function
  c) Requires in-patient hospitalisation or prolongation of existing hospitalisation
  d) Results in medical or surgical intervention to prevent permanent impairment to a body structure or body function
- An event which leads to foetal distress, foetal death or a congenital abnormality or birth defect

11 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

11.1 Sample size

The sample size calculation is based on the hypothesis that the incidence of symptomatic adjacent disc disease at 2 years after cervical disc prosthesis is equal to anterior discectomy with or without interbody fusion. Symptomatic adjacent level disease is defined as new symptoms (e.g. radicular, medular, or neck pain) referable to a motion segment adjacent to the site of previous surgery. Based on the literature, the annual incidence of symptomatic adjacent disc disease after anterior discectomy with fusion (ACDF) and anterior discectomy with disc prosthesis (ACDP) is 7% and 0.65% respectively. However, in that trial only 74 patients underwent disc arthroplasty and the probability of adjacent disc degeneration may very well be higher. Therefore, in our study, we assume an annual incidence of adjacent disc degeneration of 2% after arthroplasty and 7% after interbody fusion for the power calculations. We require a power of 90%, a significance level of 0.05 and assume a committed
accrual duration of 3 years. We plan a group sequential design with 2 interim analyses. The East software (version 5) is used for the design of this study. The assumptions (2% vs 7% to be detected) correspond to a Hazard Ratio of 0.28. With an accrual of 150 patients per year during 3 years, the required power is attained for a two-group comparison. Since we intend to perform two 2-group comparisons separately, we need 1.5*450=675 patients in total. The interim analyses are performed only for the main comparison of ACDF versus ACDP. Stopping is allowed for futility as well as efficacy.

If we would assume the 2% vs 7% to be the “truth”, the maximum study duration would be 3.5 years. Under H0 the expected total study duration would be 2.4 and under H1 3 years.

However, we feel that although there is some evidence for the 7% response rate, the trial should be designed in such a way that even with a more modest difference between the 2 groups, power is maintained, although the study duration increases (without increase in accrual) since the precision of the published estimates does not warrant a situation where the trial’s power would crucially depend on the 7% estimate:

For a difference of 2% vs 6% we have a maximum duration of 4.2 years and for a difference of 3% vs 6% we have a maximum duration of nearly 7 years.
Since powering against 2% vs 6% only increases the maximum study duration by 6 months while increasing the expected study duration under H1 also by 6 months, the interim (and final) analyses are based on a guarantee of sufficient power for the 2% vs 6% detection.

The stopping rules are as follows:

Interim analyses after 15, 30 and finally 46 events; i.e. after 276, 394 resp 450 subjects having been accrued; to be expected after 1.8, 2.6 resp 3.2 years given the assumptions of 2% resp 6% event rate. The actual moment of interim analyses is based on the information fraction, not on a prespecified point in time. The boundary chart for the decision on stopping for futility resp efficacy is the following:

Or, equivalently, on a Hazard Ratio scale:

Further information on characteristics of this sequential design is stored in the East software realization of this design (conditional power plots; accrual plots etc) and all characteristics are fixed as of start of study.
675 patients need to be included. Assuming 10% lost to follow-up, a total of 750 patients will be needed.

With the intended number of patients to be randomised, we can also evaluate the clinical outcome and self-assessment measured by the Neck Disability Index (secondary outcome). According to the literature, in general, 60% of the patients have an excellent outcome with no complaints. We define 20% better outcome measured by NDI as a clinically relevant benefit to justify cervical disc prosthesis (30 versus 25 points on the NDI). With a power of 90%, a significance level of 0.05 and a standard deviation of 9 (based on independent data), a two-sided two-sample t-test analysis will need 70 patients in each group, which is a small proportion of the total amount of patients needed for the primary objective(s).

11.2 Data Analysis

The data will be analysed according to the stopping rules outlined above, i.e. after approx 1.8, 2.6 and 3.2 years under H0 and 2.2, 3.2 and 4.2 years under H1. The actual analysis times depend on the number of events observed (15, 30 and 45). This establishes an answer to the main objectives in terms of the comparison of ADCF to ADCP. Long-term analyses of all results will be conducted irrespective of an early achievement of futility or efficacy establishing a comparison at 52, 104, 156, 208 and 260 weeks. However, these analyses will be performed after the final analysis of the trial has reached the conclusion of efficacy or futility. For all analyses, assessments performed at the first outpatient visit (visit # 1 and 2) will be taken as baseline. Baseline comparability will be analysed by descriptive statistics to determine whether randomisation was successful. Baseline measurements will be used as covariates in the analyses to increase power. Differences in outcome measures between the 2 pairs of groups, together with 95% confidence intervals, will be calculated. All data are analysed according the “intent-to-treat principle”.

The primary research objective will be tested using two t-tests, one for the comparison to discectomy with, and one to without interbody fusion. In case of homogeneity of effects, a pooled effect (adjusting for interbody fusion) will be reported. Otherwise the two analyses will be reported separately.

A repeated measurements analysis of variance for the primary outcome measure (AADD) will also be performed in order to compare the evolving patterns in AADD over time.

In addition, an explorative (but pre-specified!) subgroup analysis is conducted to investigate whether the treatment effect varies over specific subgroups of patients.

Data will be stored via the internet-based secure data management system “ProMISE” of the department of Medical Statistics and Bioinformatics. The analyses will be carried out using appropriate statistical software (e.g. SPSS).
11.3 Cost-effectiveness analysis

The economic evaluation will compare differences in societal costs to differences in the primary outcome measure (NDI) and in quality adjusted life years (QALYs). In the primary analysis QALYs will be calculated from the EQ-5D, in secondary analyses also from the SF-6D and VAS. Group averages will be statistically compared using one-way ANOVA and net-benefit analysis will be used to compare costs to patient outcome. Sensitivity analyses will be performed on (1) the intervention costs, (2) societal versus health care perspective, and (3) the applied utility measure (EQ-5D, SF-6D or VAS). A time-horizon of five years will be used, with discounting for both costs and QALYs.

11.4 Subgroup analysis

An explorative subgroup analysis will be conducted to investigate whether the treatment effect varies over specific subgroups of patients. Subgroups will be defined beforehand based on the following variables: age, gender, history of neck pain, body mass index, education, lordotic neck curvature, uncovertebral osteofytes, and disc height.

The following clinical comparisons are anticipated and will be assessed by testing the corresponding null-hypotheses using an appropriate interaction term between the subgroup variable and the randomisation variable.

- Younger patients (< 40 years) have more benefit with disc prosthesis than older patients.
- Women have less benefit with disc prosthesis than men.
- Patients with a long history of neck pain have more benefit with disc prosthesis.
- Patients with higher education have more benefit with disc prosthesis than patients with less education.
- Patients with uncovertebral osteofytes have less benefit with disc prosthesis.
- Patients with BMI > 30 have less benefit of disc prosthesis than patients with BMI < 30.
- Patients with a straight neck have less benefit of disc prosthesis than patients with a lordotic neck.
- Patients with large disc height (> 5 mm) have more benefit with disc prosthesis than patients with small disc height (≤ 5 mm).

The analyses are performed using a linear regression model (extending the primary analysis with an interaction term) at 1 year as well as a repeated measurements analysis of variance.

12 ETHICAL CONSIDERATIONS

12.1 Ethics Committee approval

Prior to initiation of this study, the investigator must submit the protocol, patient information sheet, patient informed consent and any other documentation as
required to the appropriate EC for review and approval. The investigator, and any other member of the investigation team, if also a member of the EC, must not participate in the decision-making. A signed and dated letter identifying the members of the EC reviewing this protocol will be requested.

12.2 Patient Information and Informed Consent

It is the investigator's responsibility to obtain written Informed Consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the project and before any project procedures commence. The patient should be given a copy of the Patient Information Sheet and Informed Consent Form in their native language. The original copy of the signed and dated Informed Consent must be retained in the institution’s records, and is subject to inspection by representatives of the sponsor, or representatives from regulatory agencies. Patients may also be asked to sign the standard operation consent forms produced by the hospital.

12.3 Declaration of Helsinki

The investigator will ensure that this project is conducted in full conformity with the current revision of the 2008 Declaration of Seoul (see Appendix 1).

12.4 Good Clinical Practice

The project will be conducted according to the protocol, Annex 10 of the Medical Device Directive 93/42/EEC, ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects) and to Standard Operating Procedures (SOPs) that meet the current guidelines laid down by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical trials.

12.5 Independent physician

In any case the patient can contact the independent physician. The assigned independent physician is Prof. Dr. F.R. Rosendaal (epidemiologist, Leiden University Medical Center).

12.6 Insurance

Clinical study insurance for patients will be obtained in accordance with the guidelines of the Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk onderzoek met Mensen (WMO)).
12.7 Contact with General Practitioner

It is the investigator's responsibility to inform the patient's General Practitioner (GP) (where applicable) by letter that the patient is taking part in the project provided the patient agrees to this, and information to this effect is included in the Patient Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

12.8 Patients' Confidentiality

The investigator must ensure that the subject’s privacy is maintained at all times. On the CRF or other documents submitted to the sponsors, patients will be identified by their subject project number only. Documents that are not submitted to the sponsor (for example, signed Informed Consent Forms) should be kept in a strictly confidential file by the investigator.

The investigator will permit authorised representatives of the sponsor, regulatory agencies and ethics committees to review the portion of the subject's medical record that is directly related to the project. As part of the required content of Informed Consent, the subject must be informed that his/her records will be reviewed in this manner.

12.9 Data Protection

All personnel involved in the project will observe or work within the confines of the European Data Protection Directive as interpreted by each country's laws.

12.10 End of Project

The patient’s participation in the project will end following completion of week 260.

13 ADMINISTRATIVE OBLIGATIONS

13.1 Source Data

All hospital records, laboratory reports, radiographic films, MRI and CT images, and questionnaires are considered source data.

The investigator/institution will permit trial-related monitoring, audits and regulatory inspection providing direct access to source documents.
13.2 Data Collection and Processing

All CRF’s will be completed using a black ballpoint pen, and entries must be legible. Errors should be crossed by a single line but not obliterated, the correction inserted, and the change initialled and dated by the investigator or an authorised member of the project staff. In addition, the instructions “Do not erase or type over errors” and “Do not use correction fluid or tape” will be stipulated in the CRF.

The Principal Investigator or a co-investigator will sign and date at the indicated places of the CRF. This signature will indicate a thorough inspection of the data on the CRF has been made, and it will certify the contents of the form.

All data will be entered into a web-based secure data management system (ProMISE) developed at the Department of Biostatistics and BioInformatics. Automated validation checks are implemented in the dedicated project to help identify missing data, out-of-range data and other data inconsistencies during data entry. Adverse events can be reported by the responsible clinicians directly via a separate web-based SAE/SUSAR form. A data manager will be responsible for regular quality checks of the data during the entire conduct of the trial. The database will contain the local hospital identification code of the patient for verification purposes by the local (treating) physician but no other identifiers. The date of birth will be coded as calendar year only. The study id (UIC) will be the only identification of the patient in the database. Access to the database at the individual level is restricted to the PI, the statistician and the central data manager. All accesses to the database are logged. All modifications of data are logged with time-stamp, username and IP-address.

Quality reports will be produced periodically. No comparisons between the subgroups will be made in any way until data collection is closed.

14 DURATION OF INVESTIGATION

- Start inclusion: January 2010
- Total included patients: 750
- End inclusion: January 2013
- End investigation: January 2018

15 ADDITIONAL DOCUMENTS

15.1 Declaration of Helsinki
15.2 VAS
15.3 NDI
15.4 McGill Pain Questionnaire
15.5 Patient Informed Consent form
15.6 Patient information brochure
15.7 CRF’s
REFERENCES