SURGICAL VERSUS CONSERVATIVE TREATMENT OF ODONTOID FRACTURES IN THE ELDERLY: A PROSPECTIVE COHORT STUDY

Department of Neurosurgery
Leiden University Medical Centre
Version 3 - April 2013
SURGICAL VERSUS CONSERVATIVE TREATMENT OF ODONTOID FRACTURES IN THE ELDERLY: A PROSPECTIVE COHORT STUDY

<table>
<thead>
<tr>
<th>Acronym</th>
<th>INNOVATE Trial - InteNational study on Odontoid frActure Treatment in the Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>C.L.A.M. Vleggeert-Lankamp, MD, PhD Neurosurgeon</td>
</tr>
<tr>
<td></td>
<td>Telephone: +31 71526 2109 / Fax: +31 715248221</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:cvleggeert@lumc.nl">cvleggeert@lumc.nl</a></td>
</tr>
<tr>
<td>Project Coordinator</td>
<td>J.G.J. Huybregts, PhD student Telephone: +31 71526 1490</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:j.g.j.huybregts@lumc.nl">j.g.j.huybregts@lumc.nl</a></td>
</tr>
<tr>
<td>Epidemiologist</td>
<td>W.C.H. Jacobs, PhD E-mail: <a href="mailto:w.c.h.jacobs@lumc.nl">w.c.h.jacobs@lumc.nl</a></td>
</tr>
<tr>
<td>Head of Department</td>
<td>W.C. Peul, MD, PhD Neurosurgeon E-mail: <a href="mailto:w.c.peul@lumc.nl">w.c.peul@lumc.nl</a></td>
</tr>
<tr>
<td>Project Secretariat</td>
<td>Spine Intervention Prognostic Study (SIPS) Group Telephone: +31 71526 2144</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:sips@lumc.nl">sips@lumc.nl</a></td>
</tr>
<tr>
<td>Independent Physician</td>
<td>F.R. Rosendaal, MD, PhD Telephone: +31 715264037 / Fax: +31 715266994</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:f.r.rosendaal@lumc.nl">f.r.rosendaal@lumc.nl</a></td>
</tr>
<tr>
<td>Sponsor</td>
<td>EuroSpine - Start-up Grant</td>
</tr>
<tr>
<td>Trial Website</td>
<td><a href="http://www.lumc.nl/innovate">http://www.lumc.nl/innovate</a></td>
</tr>
</tbody>
</table>
Participating Centres

- Leiden University Medical Centre, The Netherlands, cvlegeert@lumc.nl
- Medical Centre Haaglanden, The Netherlands, m.arts@mchaaglanden.nl
- University Medical Centre Nijmegen, The Netherlands, r.bartels@nch.umcn.nl
- University Medical Centre Groningen, The Netherlands, m.h.coppes@nchir.umcg.nl
- VU Medical Centre, The Netherlands, d.noske@vumc.nl
- Academic Medical Centre Amsterdam, The Netherlands, g.j.bouma@amc.uva.nl
- University Medical Centre Utrecht, The Netherlands, f.c.oner@umcutrecht.nl, w.b.m.slooff@umcutrecht.nl
- Neurochirurgische Klinik der Technischen Universität München, Germany, bernhard.meyer@lrz.tu-muenchen.de
- The National Hospital for Neurology and Neurosurgery, Queen Square London, Great Britain, athcasey@doctors.org.uk
- Sahlgrenska University Hospital, Sweden, rune.hedlund@vgregion.se, helena.brisby@vgregion.se
- Universitäres Lehrkrankenhaus Feldkirch, Austria, michael.osti@lkhf.at
- University Hospital Leuven, Belgium, bart.depreitere@uzleuven.be
- University of Leeds, Great Britain, jake.timothy@leedsth.hs.uk
- Institute of Neurosurgery, Catholic University, Largo Gemelli, Rome, Italy, mvisocchi@hotmail.com
- Spine Unit of the Vall d’Hebron University Hospital in Barcelona, Pellise, 24361fpu@comb.es
LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR  ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)

METC  Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)

Sponsor  The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

WMO  Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

NDI  Neck Disability Index

CT  Computed Tomography

MDI  Myelopathy Disability Index

VAS  Visual Analogue Scale

SF-36  Short Form 36 Health Survey

EQ-5D  EuroQol 5 Dimensions; generic measure of health

DS14  Standard assessment of negative affectivity, social inhibition, and type D personality

IPQ-K  Illness Perception Questionnaire
TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE .................................................................................. 7
2. OBJECTIVES .................................................................................................................. 8
3. STUDY DESIGN ............................................................................................................ 9
4. STUDY POPULATION ..................................................................................................... 11
   4.1 Population (base) ....................................................................................................... 11
   4.2 Inclusion criteria ....................................................................................................... 12
   4.3 Exclusion criteria ...................................................................................................... 12
   4.4 Sample size calculation .......................................................................................... 13
5. TREATMENT OF SUBJECTS ....................................................................................... 14
   5.1 Surgical treatment ................................................................................................. 14
   5.2 Conservative treatment .......................................................................................... 14
6. METHODS ..................................................................................................................... 15
   6.1 Study parameters/endpoints ................................................................................... 15
       6.1.1 Main study parameter/endpoint ...................................................................... 15
       6.1.2 Secondary study parameters/endpoints .......................................................... 15
   6.2 Study procedures .................................................................................................... 16
       6.2.1 Baseline ........................................................................................................... 16
       6.2.2 Planned follow-up moments ......................................................................... 17
   6.3 Withdrawal of individual subjects ......................................................................... 19
   6.4 Replacement of individual subjects after withdrawal ............................................ 20
   6.5 Follow-up of subjects withdrawn from treatment ................................................... 20
7. SAFETY REPORTING ..................................................................................................... 21
   7.1 Section 10 WMO event .......................................................................................... 21
   7.2 Adverse and serious adverse events ..................................................................... 21
   7.3 Follow-up of adverse events .................................................................................. 21
8. STATISTICAL ANALYSIS ............................................................................................. 22
   8.1 Descriptive statistics .............................................................................................. 22
   8.2 Univariate analysis ................................................................................................. 22
   8.3 Multivariate analysis ............................................................................................. 22
9. ETHICAL CONSIDERATIONS ....................................................................................... 23
   9.1 Regulation statement .............................................................................................. 23
   9.2 Recruitment and consent ....................................................................................... 23
   9.3 Benefits and risks assessment, group relatedness .................................................... 23
   9.4 Compensation for injury ....................................................................................... 23
10. ADMINISTRATIVE ASPECTS AND PUBLICATION .................................................. 24
    10.1 Handling and storage of data and documents ....................................................... 24
    10.2 Amendments ........................................................................................................ 24
    10.3 Annual progress report ....................................................................................... 24
    10.4 End of study report .............................................................................................. 24
    10.5 Public disclosure and publication policy ............................................................. 25
11. REFERENCES ............................................................................................................... 26
SUMMARY

Rationale: Odontoid fractures are the most common cervical spine fractures in the elderly and their prevalence is expected to increase progressively. However, the optimal treatment of this condition in the elderly is still subject to controversy.

Objective: The goal of this prospective cohort study is to assess fracture union/stability and clinical outcome after surgical and conservative treatments of odontoid fractures in the elderly patient (≥55 years). Additionally, subgroup analysis will be carried out (e.g. for patient age, osteoporosis) and prognostic factors will be identified.

Study design: A prospective cohort study with two parallel groups.

Study population: Patients suffering from acute type II/III odontoid fractures and aged at least 55 years.

Intervention (if applicable): Treatment will be based on the treating surgeon’s preference and can be either surgical or conservative.

Main study parameters/endpoints: Primary outcome will be a combination of fracture healing and clinical outcome at 52 weeks after the start of the treatment. Fracture healing will be assessed with computed tomography imaging and dynamic X-ray, focusing on both osseous union and fracture stability. Clinical outcome will we scored by the Neck Disability Index (NDI).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participating in this observational study will not put patients in greater risk, as treatment and follow-up assessments will not differ from standard care. Additional assessment of outcomes will be carried out with questionnaires which pose no extra risk for participants. Participating patients will be asked to return for follow-up purposes five times in total (at 6, 12, 26, 52 and 104 weeks). The study will be conducted in accordance with the Declaration of Helsinki.
1. INTRODUCTION AND RATIONALE

Odontoid fractures are the most common cervical spine fractures in the elderly. As the population ages, odontoid fractures will become increasingly relevant to clinical practice. The choice between surgical or conservative treatment of this condition in this age group is still subject to controversy. The general presumption is that a surgical intervention leads to a stable cervical spine. However, the condition of the patient may deteriorate by undergoing (major) cervical spine surgery. Especially in the very old patient (≥80 years of age), a surgical intervention leads to significant risks for the patient. A conservative treatment is often proposed to avoid the complications that may accompany spine surgery. However, this may result in non-union and prolonged instability, requiring secondary surgery. This unnecessarily lengthens treatment duration and, worse, often causes significant deterioration of the cervical spine anatomy. On the other hand, there are also patients that recover clinically well and can abandon their stiff neck collar, although CT does not demonstrate a satisfactory union. Thus, the outcome parameter, union, that is often used in literature, may not accurately reflect the clinical situation and its consequences.

Currently available literature concerns only retrospective studies. These studies are all of limited quality and most did not focus on elderly patients. Grounds for chosen treatments are generally unknown and groups may not be comparable. In the vast majority of published studies, only a small number of patients were included. Debate remains as to whether non-union can lead to complaints in the patient. Consequently, no consensus exists as to whether the goal of treatment should be osseous union, fracture stability or favorable clinical outcome and how outcome should be measured. Based on a recent review of the available literature carried out by the investigators, no strong recommendations can be made as to what the optimal treatment of this condition is.

The goal of this study is to prospectively assess fracture healing and clinical outcome after surgical and conservative treatment of type II/III odontoid fractures in the elderly patient. A study in which the radiological and clinical condition of both surgically and conservatively treated patients is well monitored, may lead to better decisions in the treatment of odontoid fractures in the elderly. Ideally, the subgroup analysis offers prognostic factors that can predict the success of either a surgical or conservative treatment. The outcome of this study will yield valuable information regarding the effectiveness of treatment for odontoid fractures in the elderly patient. The influence of patient age (≥55-80 and ≥80) on treatment outcome will particularly be studied.
2. OBJECTIVES

Primary Objective: To assess clinical outcome and fracture union/stability after surgical and conservative treatments for type II/III odontoid fractures in the elderly patient (≥55 years).

Secondary Objective(s): To identify the influence of patient age on treatment outcome. Furthermore, prognostic factors will be identified and predefined secondary/subgroup analysis will be carried out based on:

- Reasons for starting surgical or conservative treatment
- Myelopathy Disability Index
- Severity of VAS neck pain
- SF-36
- EQ-5D
- Personality (assessed using DS14 and IPQ-K)
- Likert
- Fracture displacement
- Osteoporosis in C2
- Degeneration in C0-C2 joints
- Pseudoarthrosis
3. STUDY DESIGN

The INNOVATE trial is a prospective, comparative cohort study with two parallel groups. Patients suffering from acute type II and III odontoid fractures and who are over 55 years of age will be included. A multicentre study is necessary to include the required number of patients in the proposed time frame. All participating hospitals are individually responsible for the treatment applied. At admission and follow-up moments, patients will be seen by their treating physician.

Primary outcome:
- Fracture healing; scored by assessing union (union or non-union) and stability (stable or unstable) at 52 weeks after start of treatment.
  - Union will be defined by evidence of bone trabeculae crossing the fracture site and absence of sclerotic borders adjacent to the fracture site, assessed using CT.
  - Fracture stability will be assessed using cervical dynamic X-rays in lateral projection. A maximum of 2 mm movement at the fracture site is considered stable, over 2 mm movement at the fracture site is considered unstable.
- Clinical outcome; scored by the Neck Disability Index at 52 weeks after start of treatment

Secondary outcomes:
clinical:
- Myelopathy Disability Index
- VAS neck pain score
- SF-36
- EQ-5D
- DS14 (psychometric properties)
- IPQ-K (illness perception)
- Likert

Radiological:
- Fracture displacement and direction
- Grade of osteoporosis in C2
- Grade of degeneration in C0-C2 joint
- Pseudoarthrosis

General
- Complications
- Reinterventions
- Secondary surgery
- Surgery after failed conservative treatment

Figure 1. Schematic overview of study design
4. STUDY POPULATION

4.1 Population (base)

Patients of at least 55 years of age suffering from acute type II or III odontoid fractures who are admitted to a participating centre and are mentally competent will be included.

The following centres participate in the study:

- Neurosurgery, Leiden University Medical Centre, The Netherlands, cvleggeert@lumc.nl
- Neurosurgery, Medical Centre Haaglanden, The Netherlands, m.arts@mchaaglanden.nl
- Neurosurgery, University Medical Centre Nijmegen, The Netherlands, r.bartels@nch.umcn.nl
- Neurosurgery, University Medical Centre Groningen, The Netherlands, m.h.coppes@nchir.umcg.nl
- Neurosurgery, VU Medical Centre, The Netherlands, d.noske@vumc.nl
- Neurosurgery, Academic Medical Centre Amsterdam, The Netherlands, g.j.bouma@amc.uva.nl
- Orthopaedics and Neurosurgery, University Medical Centre Utrecht, The Netherlands, f.c.oner@umcutrecht.nl, w.b.m.slooff@umcutrecht.nl
- Neurosurgery, Neurochirurgische Klinik der Technischen Universität München, Germany, bernhard.meyer@lrz.tu-muenchen.de
- Neurosurgery, The National Hospital for Neurology and Neurosurgery, Queen Square London, Great Britain, athcasey@doctors.org.uk
- Orthopaedics, Sahlgrenska University Hospital, Sweden, rune.hedlund@vgregion.se, helena.brisby@vgregion.se
- Traumasurgery, Universitäres Lehrkrankenhaus Feldkirch, Austria, michael.osti@lkhf.at
- Neurosurgery, University Hospital Leuven, Belgium, bart.depreitere@uzleuven.be
- Neurosurgery, University of Leeds, Great Britain, jake.timothy@leedsth.hs.uk
- Neurosurgery, Institute of Neurosurgery, Catholic University, Largo Gemelli, Rome, Italy, mvisocchi@hotmail.com
- Orthopaedics, Spine Unit of the Vall d’Hebron University Hospital in Barcelona, Pellise, 24361fpu@comb.es
Participating institutions and surgeons are all able to facilitate/perform both surgical and conservative treatments. The coordination of the study will be carried out from the Leiden University Medical Centre, which is experienced in conducting multicentre national and international studies. The Spine Intervention Prognostic Study Group has a study group, established research databases, and a group of study nurses available. The research nurses will be available for surgeons who have questions about the study protocol or the treatment of individual subjects.

Based on the number of participating centres, the estimated time needed to complete recruitment of the required sample size (275 patients) will be 36 months. The last follow-up is 104 weeks after the inclusion of the last patient.

Logistical preparations January 2012 – July 2012
Start Inclusion August 1, 2012
Last inclusion August 1, 2015
Last Follow-up August 1, 2017
Report December 31, 2017

4.2 Inclusion criteria

- At least 55 years old
- Acute type II and III odontoid fracture based on the classification by Anderson and d’Alonzo (possibly in combination with other fractures); diagnosed using computed tomography
- Less than two weeks post injury
- Informed consent

4.3 Exclusion criteria

- Rheumatoid arthritis
- Ankylosing spondylitis
- Previous treatment for odontoid fracture
- Communication with patient is hampered (e.g. language barrier, severe cognitive impairment, coma)
4.4 Sample size calculation

Based on the recent literature review, the estimated possible difference in fracture union between the groups is 41% and in fracture stability this difference is 21%\(^1\). For both union and stability, however, a smaller difference of 20% would be clinically relevant and the study is powered to assess this difference. For the NDI, inadequate information was available, but a 7.5 point difference (on a 50 point scale) is generally accepted as a minimally clinically important difference with a SD of approximately 10 in various psychometric studies\(^2\)\(^-\)\(^5\). Furthermore, it is expected that the number of patients that will be treated surgically will be twice the number of patients that are treated conservatively (2:1). Since three primary outcome hypotheses will be tested, the significance level (\(\alpha\)) has to be divided by three. Based on the primary outcome parameters, the required sample size, assuming \(\alpha = 0.05/3 = 0.0167\) (two-sided) and \(\beta = 0.20\) (80% power) and an expected drop out rate of 10%, is 275 for union, 198 for stability and 208 for the NDI. In conclusion, 275 will need to be recruited in order to give a reliable conclusion to the comparison of union, stability and clinical outcome between the surgically and conservatively treated groups.
5. TREATMENT OF SUBJECTS

Based on the treating surgeon's and patient's shared decision, surgical or conservative treatment will be started and documented. During follow-up appointments demographic, radiological and clinical data will be gathered. Patients will also be sent questionnaires to answer at home. Questionnaires will focus on pain intensity, general wellbeing and illness-related inconveniences.

5.1 Surgical treatment

Surgical treatment can be carried out by either an anterior or posterior approach. In an anterior approach, a single or double odontoid screw is placed through the corpus of C2 into the odontoid process to directly stabilise the fracture. In the posterior approach, fusion of the C1-C2 vertebrae is carried out, thereby indirectly immobilising the odontoid process as well. The posterior technique is sometimes extended cranially to C0 or caudally to C3 or lower, possibly leading to increased stability but further limiting the cervical range of motion.

5.2 Conservative treatment

Conservative treatment involves a variety of devices by which a patient's cervical spinal column is externally immobilised. Non-surgical immobilisation of the cervical spine will be carried out according to the treating physician's preference.
6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

- Fracture healing, assessing union (union or non-union) and stability (stable or unstable) at 52 weeks after start of treatment.
  - Union will be defined by evidence of bone trabeculae crossing the fracture site and absence of sclerotic borders adjacent to the fracture site, assessed using CT.
  - Fracture stability will be assessed using cervical dynamic X-rays in lateral projection. A maximum of 2 mm movement at the fracture site is considered stable, over 2 mm movement at the fracture site is considered unstable.
- Clinical outcome; scored by the Neck Disability Index at 52 weeks after start of treatment

6.1.2 Secondary study parameters/endpoints

Clinical:
- Myelopathy Disability Index
- VAS neck pain score
- SF-36
- EQ-5D
- DS14 (psychometric properties)
- IPQ-K (illness perception)
- Likert

Radiological:
- Fracture displacement
- Grade of osteoporosis in C2
- Grade of degeneration in C0-C2 joint
- Pseudoarthrosis
6.2 Study procedures

Apart from the applied treatment started by the treating surgeon, patients will be handled and followed-up similarly. Extensive data will be gathered upon inclusion (baseline). Follow-up treatment will be according to usual care (including possible secondary surgery). Follow-up assessment will involve the evaluation of fracture healing and the patient’s clinical status. Five follow-up moments are scheduled for all patients. If an individual patient’s condition does not improve or worsens, more contact moments will be planned.

6.2.1 Baseline

**General:**
- Age, gender, length, mass
- Mechanism of injury
- Neurological deficits
- Associated injuries
- Pre-existing systemic diseases
- Surgical risk factors
- Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS neck pain score, SF-36, EQ-5D
- Motivation of choice of treatment by the treating surgeon (including the choice of anterior or posterior surgery, and whether or not this depended on the surgeon’s familiarity with the procedure)
- Degree of conviction of the surgeon on the correctness of the treatment applied

**Fracture assessment:**
- Fracture classification according to Anderson and d’Alonzo
- Fracture classification according to Grauer’s modification
• Fracture displacement (mm) and its direction (anterior, posterior, lateral, anterior-lateral, posterior-lateral) by drawing lines along the posterior and lateral aspects of the odontoid process and the caudal body of C2

• Grading of osteoporosis in C2\textsuperscript{6,7}
  o None: normal trabecular pattern with normal cortical thickness
  o Mild: decrease in the amount of trabeculae with no areas of holes and normal cortical thickness
  o Moderate: absent trabeculae (holes) involving less than 25% of the transverse diameter of the bone with cortical thinning
  o Severe: absent trabeculae (holes) involving more than 50% of the transverse diameter of the bone with cortical thinning

• Grading of degeneration in C0-C2 joints\textsuperscript{6,7}
  o None: normal joint space with no osteophyte formation
  o Mild: narrowed joint space or normal joint space with osteophyte formation
  o Moderate: obliterated joint space with or without osteophyte formation
  o Severe: completely obliterated joint space, ankylosis or fusion of the joint

6.2.2 Planned follow-up moments

Immediately after start of treatment

For all patients:
• Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS, SF-36, EQ-5D
• Complications (if applicable)
  For surgically treated patients:
• Collection of intra- and/or post operation radiographs/computed tomography images to assess success of surgical intervention (if available)
• Details on surgical treatment
  For conservatively treated patients:
• Details on immobilisation
Moment 1: Six weeks after start of treatment

Neurological/clinical status:
- Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS, SF-36, EQ-5D, DS14, IPQ-K, Likert
- Complications (if applicable)

Moment 2: Twelve weeks after start of treatment

Neurological/clinical status (questionnaires can be answered at home):
- Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS, SF-36, EQ-5D, DS14, IPQ-K, Likert
- Complications (if applicable)
  Fracture assessment:
  - CT to assess union

Moment 3: Twenty-six weeks after start of treatment

Neurological/clinical status:
- Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS, SF-36, EQ-5D, DS14, IPQ-K, Likert
- Complications (if applicable)
  Fracture assessment:
  - Cervical dynamic X-ray to assess fracture stability (when possible)
  - CT to assess union (when indicated)

Moment 4: Fifty-two weeks after start of treatment

Neurological/clinical status:
- Questionnaires: Neck Disability Index (primary outcome), Myelopathy Disability Index, VAS, SF-36, EQ5D, DS14, IPQ-K, Likert
- Complications (if applicable)
  Fracture assessment:
  - Cervical dynamic X-ray to assess fracture stability
  - CT to assess union (primary outcome)
Moment 5: One-hundred-and-four weeks

Neurological/clinical status:
- Questionnaires: Neck Disability Index, Myelopathy Disability Index, VAS, SF-36, EQ5D, DS14, IPQ-K, Likert
- Complications (if applicable)

Fracture assessment:
- Cervical dynamic X-ray to assess fracture stability

<table>
<thead>
<tr>
<th>OVERVIEW</th>
<th>Admission</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intake</td>
<td>Immediately after start of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Weeks</td>
</tr>
<tr>
<td>CRF 1. Intake surgeon</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CRF 2. Baseline assessment of CT</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CRF 3. Applied treatment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CRF 4. Follow-up surgeon</td>
<td>X*</td>
<td>X</td>
</tr>
<tr>
<td>CRF 5. Complications of surgery</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>CRF 6. Secondary surgery</td>
<td>X*</td>
<td>X*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionnaires (patient)</th>
<th>Admission</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF A. NDI</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF B. MDI</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF C. VAS Neck Pain</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF D. SF-36</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF E. EQ-5D</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF F. DS14</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF G. IPQ-K</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>CRF H. Likert</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>Radiology</td>
<td>Dynamic X-ray</td>
<td>X</td>
</tr>
<tr>
<td>CT</td>
<td>X</td>
<td>X**</td>
</tr>
</tbody>
</table>

* When indicated
** In case of surgical treatment only, three days after surgery
X Will be sent from LUMC to patient’s home

Figure 2. Overview of scheduled follow-up moments

6.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. As this is an observational study, this will only have influence on the study related assessments. The investigator can decide to withdraw a subject from the study for urgent medical reasons.
6.4 Replacement of individual subjects after withdrawal

Individual subject withdrawn from the study will not be replaced. In the sample size calculation was accounted for a drop out rate of 10%.

6.5 Follow-up of subjects withdrawn from treatment

Data analysis will be carried out based on the intention-to-treat principle. Cross-over cases (surgery after failed conservative treatment) will be analysed among the original treatment group. The reasons for this cross-over will be studied and reported.
7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

7.2 Adverse and serious adverse events

All participating hospitals are individually responsible for the treatment applied.

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the applied treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients’ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as An unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

7.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
8. STATISTICAL ANALYSIS

8.1 Descriptive statistics

Mean, median and standard deviations or median and ranges, if appropriate in case of skewed distributions, of descriptive parameters of primary and secondary outcomes will be reported.

8.2 Univariate analysis

Univariate analysis will be carried out using $\chi^2$-tests for dichotomised outcomes and T-tests for continuous outcomes. Intention-to-treat analysis will be used for cases that crossed over to other interventions.

*Primary analysis:*

T-test will be used to test for differences between groups on NDI improvement.
$X^2$-test will be used to test for differences between groups on union and stability.

*Secondary analysis:*

$X^2$ test will be used to analyse the difference in dichotomised NDI. NDI will be dichotomised using the criterium of the minimal clinically important change (improvement) of 7.5 points out of 50.
The relation between radiological parameters (union and stability) and NDI will be analysed by comparing the average NDI improvement for patients that acquired union/stability with those that did not.

8.3 Multivariate analysis

Multivariate analyses will be carried out using regression models using dichotomised NDI, union and stability as dependent variables and with the secondary outcome parameters as independent variables and covariates.
Propensity score analysis will be used to generate a model to predict the treatment received with the baseline variables.
9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients admitted to one of the participating facilities who meet the inclusion criteria will be asked to participate by the treating surgeon. The surgeon will provide the patient with the patient information letter and will answer potential questions. Patients are then asked for their informed consent, after which the baseline data will be gathered prior to the start of treatment.

9.3 Benefits and risks assessment, group relatedness

As the applied treatment will not differ from the usual care, participating patients will neither benefit nor will they be at risk by participating in this study regardless of the treatment they undergo.

9.4 Compensation for injury

Participating in this observational study does not influence the treatment applied and therefore poses no additional risks. Also, study related assessments consist of questionnaires, which do not pose extra risk for included patients. Imaging obtained for this study follows the usual care protocol and thus does not pose extra burden for the patient. For this reason, dispensation from the statutory obligation to provide insurance is requested by the accrediting METC.
10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

Patients will be given a UIC (Union International Code) number. In a secured Access database only accessible for research staff involved in the study, patients’ personal data are linked to their UIC number. All data will be securely and anonymously gathered in the studies’ ProMISe database. Data will be stored for fifteen years after the end of the study and will be accessible for the principal investigator only.

10.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator.

10.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

10.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results
of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.5 Public disclosure and publication policy

No arrangements will be made between EuroSpine, the sponsor, and the investigators concerning the public disclosure and publication of the research data. The results of the study are anticipated to be published in a peer reviewed journal.
11. REFERENCES


