THE FELIX TRIAL

Clinical Investigation Plan for:

A randomised controlled trial, comparing Surgical Decompression with an Interspinous Implant in Patients with Intermittent Neurogenic Claudication caused by Lumbar Stenosis

Primary contact:
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A Randomised, Blinded Comparison of Surgical Intervention with the Coflex™ Interspinous Implant versus Surgical Decompression for Patients with Intermittent Neurogenic Claudication caused by Lumbar Stenosis

<table>
<thead>
<tr>
<th>Study Identification:</th>
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<tbody>
<tr>
<td>Principal Investigator:</td>
<td>Dr. W.C. Peul</td>
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<tr>
<td>Sponsor:</td>
<td>Paradigm Spine/InSpine</td>
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<td>Monitor Arrangements:</td>
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<td>Data and Quality Management:</td>
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**Approval and Agreement**

By signing this page the Sponsor and Principal Investigator agree to conduct this investigation in accordance with the current investigational plan. No changes to this clinical investigation plan will be permitted without the written approval of both parties. If clinical investigation plan changes become necessary, written approval by the Investigator’s Ethics Committee will be obtained before the changes are implemented.

Principal Investigator Date

Sponsor Representative Date
# Table of Contents

1 Table of Contents 3
2 Clinical Investigation Summary 5
3 Abbreviations 7
4 Introduction 8
   4.1 Background 8
   4.2 Rationale of the Clinical Investigation 9
   4.3 Summary of Pre-Clinical Testing 9
      4.3.1 Implant Breakage or Migration 9
      4.3.2 Insertion Load 9
      4.3.3 Kinematics 10
   4.4 Summary of Previous Investigations 10
5 Device Risk Analyses and Risk Assessment 10
   5.1 General Surgical Risk Assessment 10
   5.2 Device Risk / Benefit Analysis 11
6 Objectives 11
   6.1 Hypothesis 11
   6.2 Primary Objective 11
   6.3 Secondary Objective 11
   6.4 Primary Endpoint 11
   6.5 Secondary Endpoint 11
7 Design 12
   7.1 Overall Design 12
   7.2 Number of Patients and Sites 12
   7.3 Randomisation and Blinding 12
   7.4 Variables to Be Measured 13
      7.4.1 Demographic Data 13
      7.4.2 Neurological/Clinical Investigations 13
      7.4.3 Disorder-specific outcome scores (ZCQ, MRDQ, shuttle walking test) 13
      7.4.4 SF-36 14
      7.4.5 Pain (McGill Pain Questionnaire & Vas Score for Pain) 14
      7.4.6 Perceived Recovery 15
      7.4.7 Patient Global Impression of Change 15
      7.4.8 Hospital Anxiety Depression Scale (HADS) 15
      7.4.9 Costs 15
      7.4.10 MRI 16
      7.4.11 Complications 17
      7.4.12 Re-operation Incidence 17
      7.4.13 Operative Data 17
   7.5 Timing of Analysis 17
8 Patient Selection 17
   8.1 Target Population 17
   8.2 Inclusion Criteria 17
   8.3 Exclusion Criteria 18
9 Description of the Device and Surgical Techniques 18
   9.1 Coflex™ Interspinous Implant Device 18
   9.2 Coflex™ Interspinous Implant Device - Surgical Technique 18
   9.3 Decompression – Surgical Technique 19
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4</td>
<td>19</td>
</tr>
<tr>
<td>9.5</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
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## 2 CLINICAL INVESTIGATION SUMMARY

| Title: | A Randomised, Blinded Comparison of Surgical Intervention with the Coflex™ Interspinous Implant versus Surgical Decompression for Patients with Intermittent Neurogenic Claudication caused by Lumbar Stenosis |
| Sponsor: | Paradigm Spine/InSpine |
| Clinical Phase | Randomized Controlled Trial |
| **Primary Objective:** | The effectiveness of the surgical intervention with the Coflex™ is equivalent to surgical decompression without fusion after 12 months in case of INC based on lumbar vertebral stenosis that exists for at least 3 months. |
| **Secondary Objective:** | Surgical intervention with the Coflex™ is more cost effective after 12 months than surgical decompression without fusion. Surgical intervention with the Coflex™ is more effective on short-term (8 weeks to 6 months). Surgical intervention with the Coflex™ is as effective as surgical decompression without fusion after 5 years in case of INC based on lumbar vertebral stenosis that exists for at least 3 months. |
| **Indication:** | Intermittent Neurogenic Claudication secondary to Lumbar Spinal Stenosis responsive to flexion of lumbosacral spine, with or without back pain, existing for > 3 months and failure to obtain adequate symptom relief with conservative treatment methods. |
| Investigational Design: | A prospective, randomised, blinded study comparison of two treatments. |
| Number of Patients: | A total of 386 patients will be randomised between the Coflex™ and the surgical decompression group. |
| **Target Population** | Male or female participants aged between 45-80 years who have been diagnosed with intermittent neurogenic claudication with or without back pain and failed conservative treatment. |
| **Length of Investigation:** | Patients included in this investigation will have follow-up visits at 8 weeks, 6, 12, 24 & 60 months. The recruitment period is estimated as 12 months. |
| Paradigm Spine Device/Procedure: | The Coflex™ Device
Interspinous distraction |
<table>
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<tr>
<th>Comparator Device/Procedure:</th>
<th>Surgical Decompression by laminectomy or interarcuair decompression</th>
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<tr>
<td>Clinical Performance Assessments:</td>
<td>Primary endpoint: symptoms of intermittent neurogenic claudication as measured by the Zurich Claudication Questionnaire. Secondary endpoint: Cost effectiveness as measured by the EuroQol questionnaire and costs obtained from the patient’s diary.</td>
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<tr>
<td>Safety Assessments:</td>
<td>Safety will be assessed by appropriate recording and reporting of adverse events throughout the investigation, including reoperation rates.</td>
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<td>Statistical Analysis:</td>
<td>Appropriate tests will be performed to ensure comparability between the preoperative treatment groups. Within group comparisons will be performed to evaluate improvements in scores from baseline. Between groups comparisons will be made to compare the effectiveness of the two groups.</td>
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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CEA</td>
<td>Cost effectiveness analysis</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CUA</td>
<td>Cost utility analysis</td>
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<tr>
<td>FDA</td>
<td>Food and drug administration</td>
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<tr>
<td>INC</td>
<td>Intermittent neurogenic claudication</td>
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<tr>
<td>IPD</td>
<td>Interspinous process decompression</td>
</tr>
<tr>
<td>LUMC</td>
<td>Leids Universitair Medisch Centrum</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MRDQ</td>
<td>Modified Roland disability questionnaire</td>
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<tr>
<td>SF-36</td>
<td>Short Form-36</td>
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<tr>
<td>SWT</td>
<td>Shuttle walking test</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life years</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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<td>ZCQ</td>
<td>Zurich claudication questionnaire</td>
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4 INTRODUCTION

4.1 Background

Intermittent Neurogenic Claudication (INC) is a disorder resulting from lumbar vertebral stenosis or a narrowing of the lumbar vertebral canal and is especially frequent among elderly people. The main symptoms are low back pain and irradiation of the pain in one or both legs. These complaints appear typically after walking some distance and after standing for some time; the pain in back and legs increases, the legs feel dead and can no longer be controlled. The complaints are reduced by bending the back, like sitting, bending over or squatting down. An explanation of this is that bending the back provides more space at the back of the vertebrae that leads to a reduction of the pressure on the nerve roots. This is also the reason that most patients with INC ride their bikes normally without noticeable leg and back complaints.

As a result of many years of pressure, the vertebral column of elderly people tends to show wear. Wear, or arthrosis, is a common symptom of aging that occurs to everyone, but the extent to which it occurs differs from person to person. As a reaction to arthrosis the vertebral bone will start to grow quickly and will become thicker especially at the joints, narrowing the vertebral canal. Usually the yellow ligaments have also thickened causing even less space in the narrowed vertebral canal for the spinal cord and the nerve roots. In addition the intervertebral disc and/or the vertebra may bulge out and/or the vertebrae may shift in respect to each other (spondylolisthesis).

Radiological confirmation of the clinical diagnosis is commonly performed by computed tomography (CT) scan or magnetic resonance imaging (MRI) cross sections of the lumbar vertebral column to demonstrate the presence of a narrowed vertebral canal. Normally, the cross section of the vertebral canal has a triangular shape, but in case of stenosis the vertebral bone has thickened to such an extent that the cross section has a T-shape or has even become slit-shaped.

In the first instance lumbar vertebral stenosis is treated by non-invasive methods, such as anti-inflammatory medications, physical therapy, and local injections with steroidal hormones. If symptoms continue to progress or become more painful, surgery to widen the spinal canal can be considered (surgical decompression).

The operations typically used to treat lumbar stenosis include laminectomy, laminotomy, and foraminotomy which can be combined with a spinal fusion operation. The most commonly used decompressive surgery is the laminectomy. A laminectomy involves removing the bony extensions (lamina) from the backside of the vertebral body which is causing pressure on the spinal sac and/or nerve roots. Often, only a portion of the lamina needs to be removed to relieve pressure on the nerve roots (laminotomy). At the same time, a portion of the facet joints at the sides of the lamina may also be removed since they also cause increased pressure on the central and foraminal areas. The goal of a foraminotomy is to enlarge the space where the nerve roots exit the spinal canal thus decreasing pressure on them.

The above described operations are performed under general anaesthesia and 3 to 7 days hospitalization may be required, followed by an 8-week recovery period.
There is inconclusive evidence that arthrodesis, instrumented or not, has a significant impact on symptom severity, physical function or patient satisfaction. For patients undergoing laminectomy with arthrodesis, the associated morbidity, however, increases dramatically. With success rates reported between 26% and 100% (the mean being 64%)\(^1\), surgery for degenerative lumbar stenosis is generally performed electively to improve quality of life. While patient satisfaction is an important outcome for elective surgeries, patient satisfaction after surgery for spinal stenosis has received little study. One retrospective study with an average of 4.6 years of follow-up showed that 31% of patients were dissatisfied with their operation.\(^2,3\)

In recent years a safe and effective treatment has been developed as an alternative to surgical decompression. This procedure is less invasive and is known as “Interspinous Process Decompression” (IPD) treatment. A small implant called Coflex\(^\text{TM}\) will be inserted between the spinal crests of the affected vertebral levels, which will lead to distraction of the interspace, and reduce the pressure on the nerves leading to a return to a neutral or slightly tightened position of the vertebral column.

The described treatment by IPD has been approved in Europe for nearly 4 years and has recently been approved by the USA Food and Drug Administration (FDA).

### 4.2 Rationale of the Clinical Investigation

In this investigation, it will be investigated whether the effectiveness of surgical intervention with IPD (Coflex\(^\text{TM}\)) is equivalent to surgical decompression after 12 months in people with INC. The main advantage of IPD might be a faster recovery after surgery, but after long term follow-up it is unknown if this treatment effect remains. Therefore in addition, it will be investigated whether surgical intervention with IPD is more effective than surgical decompression on short-term follow-up (8 weeks to 6 months) and whether surgical intervention with IPD is more cost-effective after 12 months than surgical decompression. A similar investigation has shown that IPD is more cost-effective for the American Model for Private Healthcare system.\(^4\)

### 4.3 Summary of Pre-Clinical Testing

#### 4.3.1 Implant Breakage or Migration

A series of expulsion tests was performed on a cadaver motion segment to determine the forces necessary to expel the IPD. A 450-pound axial load was applied to the segment. Torsional rotation was applied to the segment and the displacement load measured. The segment reached its physiological limit at approximately 15 degrees of rotation without the implant dislodging. The segment was then flexed 30 degrees and extended 30 degrees, representing the maximum range of motion that could be obtained. The implant did not dislodge or displace. The implant was then removed and the spinous processes examined. There was no apparent damage to the spinous processes. Dislodgement would most likely be associated with fracture of the spinous process. The significance of such an occurrence would be the loss of distraction at the involved segment.

#### 4.3.2 Insertion Load

A study in situ was performed to investigate the lateral failure loads of the spinous process and compare the failure loads to the loads required to insert a IPD implant. The technique used to insert the Coflex poses little risk to spinous process failure. There is ample margin of safety between the insertion loads (mean 65.6±46.2 N) and spinous process failure loads (mean 316.9±196.5 N).\(^5\)
4.3.3 Kinematics

Results in situ indicate that the flexion-extension range of motion was significantly reduced at the instrumented level. Axial rotation and lateral bending ranges of motion were not affected at the instrumented level. The range of motion in flexion-extension, axial rotation, and lateral bending at the adjacent segments was not significantly affected by the IPD. In addition, in extension, the implant significantly increased the canal area by 18%, the subarticular diameter by 50%, the canal diameter by 10%, the foraminal area by 25%, and the foraminal width by 41% indicating that the IPD prevents narrowing of the spinal canal and foramina in extension.

Results in situ indicate that the IPD does not significantly change the intradiscal pressures at the adjacent levels, yet it significantly unloads the intervertebral disc at the instrumented level in the neutral and extended positions. On basis of these results, it does not appear that the IPD causes accelerated disc degeneration at the adjacent levels. The IPD also significantly reduces the mean peak pressure, average pressure, contact area, and force at the facets at the implanted level, while these were not significantly different between the intact and implanted specimens with the exception of the contact area of the L2-L3 level.

4.4 Summary of Previous Investigations

From May of 1997 to April of 1998, ten patients with symptomatic lumbar spinal stenosis underwent implantation of the IPD. No surgical complications were observed. Patients showed clinically significant improvement in symptom severity and physical function. Overall, 80% of the patients showed some level of improvement in their symptom severity score, physical function score, walking distance, or all three. One device-related complication occurred, and symptoms recurred in one patient.

In the FDA required randomized multicentre study, surgical intervention with the IPD is compared to a non-surgical treatment. After 2 years, the IPD group shows both clinically and statistically significant improved results in comparison with the non-surgical treated group.

A European Registry includes more than 300 patients who are been treated with the IPD, from whom nearly 90 patients passed the 12 months follow-up point. Significant improvements have been seen in Zurich Claudication Questionnaire (ZCQ), Short Form-36 (SF-36) and overall patient satisfaction with their treatment.

5 Device Risk Analyses and Risk Assessment

There are two categories of risk factor for consideration here, namely that associated with general spinal surgery per se and also that associated with any specific surgical procedures linked to the instrumentation being used.

5.1 General Surgical Risk Assessment

Operative risks include anaesthetic-related problems, circulatory problems, a collapsed lung, pneumonia, blood clots, intra-operative damage to blood vessels, soft tissue, or nerves or an allergic reaction to blood products or medications such as antibiotics and anaesthetic agents. As with any major surgical procedure, cardiovascular and pulmonary complications are potential risks. In very rare instances, heart attack or death may occur. Although these complications are extremely rare, they may require additional surgery, extend the duration of surgery or extend the duration of the hospital stay.
5.2 Device Risk / Benefit Analysis
Specific potential complications of the IPD (Coflex) are dislodgement or migration of the implant, no correct positioning of the implant, fracture of the spinous process, additional surgery which could include removal of the implant, foreign body reaction, mechanical failure of the implant, failure of the implant to improve symptoms and/or function.

Complications from lumbar spine procedures including laminectomy include perioperative mortality, dural tears, deep infection, superficial infection, and deep vein thrombosis.

The benefits of spinal surgery include the potential to dramatically improve a patient’s quality of life by enabling them to become more active and take a more constructive part in society. This is achieved by the removal of the cause of their pain and through rehabilitation reduces their dependence on the medical system for long term medical treatment. Obviously the level of improvement is linked to other pre-existing medical conditions.

A device accountability log will be completed. A record of all devices shipped to each site will be maintained by the sponsor and (“a device accountability log will be completed by each site.

6 OBJECTIVES

6.1 Hypothesis
The null hypothesis of this research is that the ZCQ outcome of IPD surgery is similar to the ZCQ outcome of surgical decompression at 1 year after surgery.

The aim of the investigation is to address the following objectives in terms of patients with INC resulting from stenosis of the lumbar vertebral column:

6.2 Primary Objective
Surgical intervention with the IPD (Coflex) is as effective as surgical decompression without fusion after 1 year in case of INC based on lumbar vertebral stenosis that exists for at least 3 months.

6.3 Secondary Objective
Surgical intervention with the IPD (Coflex) is more effective after 8 weeks than surgical decompression without fusion in case of INC based on lumbar vertebral stenosis that exists for at least 3 months.
Surgical intervention with the IPD (Coflex) is more cost effective after 12 months than surgical decompression without fusion in case of INC based on lumbar vertebral stenosis that exists for at least 3 months.
Surgical intervention with the IPD (Coflex) is as effective as surgical decompression without fusion after 5 years in case of INC based on lumbar vertebral stenosis that exists for at least 3 months.

6.4 Primary Endpoint
The effectiveness will be measured with the ZCQ score.

6.5 Secondary Endpoint
Cost effectiveness as measured by the EuroQol questionnaire and costs obtained from the patient’s diary.
7 DESIGN

7.1 Overall Design
This research project will be conducted on a prospective, randomized, patient-blinded and research nurse-blinded, multicentre basis with a 5-year longitudinal follow-up with repeated measurement analysis.

7.2 Number of Patients and Sites
Participation in this investigation will be requested from all patients (45-80 years old) with a history of at least 3 months of INC, who contact the neurologist or neurosurgeon directly in one of the hospitals:

- Medical Center Haaglanden, The Hague/Leidschendam, the Netherlands
- Leiden University Medical Center, Leiden
- Rijnland ziekenhuis, Leiderdorp
- Canisius-Wilhelmina Ziekenhuis, Nijmegen, the Netherlands (recruitment & surgeries will be performed at this hospital)
- HAGA ziekenhuis, The Hague
- Sint Lucas Andreas Ziekenhuis, Amsterdam
- Vlietland Ziekenhuis, Schiedam
- Groene Hart Ziekenhuis, Gouda, the Netherlands (only recruitment)
- Reinier De Graaf Gasthuis, Delft, the Netherlands (only recruitment)
- Schieland Ziekenhuis, Schiedam, the Netherlands (only recruitment)
- Bronovo Ziekenhuis, The Hague, the Netherlands (only recruitment)

Both the surgical intervention as the decompression will be performed in the first 4 mentioned hospitals. The follow-up visit can be performed in either the hospital where the surgery was done or in the patient's local hospital.

7.3 Randomisation and Blinding
The randomization will be performed centrally at the LUMC. In the participating hospitals the research nurse will collect the patient data. All data will be collected and analyzed centrally.

Group A will be admitted to the hospital in which the procedure will be performed, normally within 4 weeks, and will undergo surgical decompression without fusion, followed by post-operative treatment specified per patient's need.

Group B will be admitted to the hospital in which the procedure will be performed, normally within 4 weeks, and will be operated on using the IPD procedure in which a Coflex is placed, followed by post-operative treatment specified per patient's need.

The randomization list will be prepared by Ronald Brand, Department of Medical Statistics, LUMC. The randomization list will be stratified centrally, using blocks in various sizes. A copy will be kept at the LUMC SIPS group. Each hospital which will perform surgery will receive a set of sequentially numbered sealed randomization envelopes.

Once an envelope has been opened and the patient leaves the investigation (for whatever reason), this envelope will no longer be used.
7.4 Variables to Be Measured

Data in respect to the following variables will be collected:

- Demographic data
- Neurological/clinical investigations
- Disorder-specific outcome scores (ZCQ, MDRQ, shuttle walking test)
- SF-36
- Pain (McGill Pain Questionnaire & Vas Score for Pain)
- Perceived Recovery
- Patient Global Impression of Change
- MRI
- Costs
- Complications
- Re-operation incidence
- Operative data

7.4.1 Demographic Data

Pre-operative per patient the following data will be recorded: date-of-birth, sex, profession, smoking habits, previous back complaints. Weight and height will be collected for the Quetelet Index/BMI, medical history and diagnosis including present medical status and medication use, INC history including (conservative) treatment and presence of spondylolisthesis with specification of grade if present.

7.4.2 Neurological/Clinical Investigations

Pre-operative a basic physical neurological examination (muscle strength, reflexes, lungs, heart, and belly) and additional assessments as required per routine practice will be performed to ensure the patient is in good condition to undergo surgery. During study visits neurological investigation will also be performed to evaluate patient’s condition.

7.4.3 Disorder-specific outcome scores (ZCQ, MDRQ, shuttle walking test)

7.4.3.1 ZCQ

The disorder-specific functional score will be the primary result measure and can be obtained by completing the ZCQ, also known as the Brigham spinal stenosis questionnaire and Swiss spinal stenosis questionnaire.\(^{13,14,16}\) The ZCQ is a validated result measuring instrument for spinal stenosis. The questionnaire consists of 3 scales:

- physical scale (consists of six questions with four possible answers)
- symptom severity scale (consists of seven questions with three possible answers)
- satisfaction scale (consists of five questions with five possible answers and will be completed only after surgery).

Each answer will be granted with a score between 1 and 4 or 5. The best score is 1, so a lower score is better than a high score. The total score of a scale will be calculated by adding up the scores of all answers and dividing the total by the number of answered questions.

The thresholds for clinical success for the domains physical function and symptom severity are a decrease of 0.5 points. The threshold for the domain satisfaction score is a score of less than 2.5 the patient is clinically successful. An overall success will require that a patient achieved at least success in two domains.\(^{16}\)

7.4.3.2 MDRQ

The 23-points MDRQ is the most widely used patient-assessed measure of health outcome for low back pain.\(^ {17,18,19,20,21}\) The patient will complete the questionnaire and the
sum of scores reflects the invalidity in daily life. The score can vary from 0 to 23 with a high score representing patients with severe complaints.

7.4.3.3 Shuttle Walking Test
The functional status of the patient can be assessed by the Shuttle Walking Test (SWT), developed originally to assess exercise tolerance in patients with chronic obstructive airway disease and those with cardiac disorders. The SWT has also been used as an outcome measure in clinical trials involving patients with chronic back pain. It is reported that the SWT needs to change by 76 m to ensure that the walking distance is changed, but large changes in the SWT can occur after surgery, and the SWT may thus provide a useful measure on an individual basis.

7.4.4 SF-36
The SF-36 will be used as the generic questionnaire. The questionnaire can be completed easily by the patient, either at home or in the waiting room. The SF-36 questionnaire has been applied and validated numerous times for intervention studies in respect with vertebral column pathology.

The questionnaire relates to the analysis of the general functional status of patients. The questions are divided in eight domains:
- physical functioning
- physical role limitations
- emotional role limitations
- social functioning
- physical pain
- general mental health
- vitality
- general health perception.
Per domain the scores of the items are added up and transformed into a scale of 0 to 100. A higher score reflects a better health condition. In addition, these 8 domains can be summarized in a physical and psychological main domain. Both main domains have been composed from eight domains, although there are large differences in the extent to which the various domains are weighted. The main domains have been construed in such manner that they have an average of 50 and a standard deviation of 10.

7.4.5 Pain (McGill Pain Questionnaire & Vas Score for Pain)
7.4.5.1 McGill Pain Questionnaire
Pain is the main complaint for the patient. Pain can be measured with numerous methods. The McGill questionnaire measures the quality aspect of pain, next to the intensity of pain. Three dimensions were distinguished:
- sensoric dimension which measures the observed characteristics of pain (time, pressure, temperature, etc)
- affective dimension which measures the stress, anxiety and autonomic reactions on pain
- evaluative dimension which measures the subjective experience of pain.

7.4.5.2 Vas Score for Pain
Next to the McGill pain questionnaire the pain intensity in legs and back are chosen as secondary effect measure next to the quality of life.
The pain intensity in both legs and back will be measured with the 100 mm horizontal VAS. The two poles of the line are “no pain” at 0 mm and “the most terrible pain I can imagine” at 100 mm. The resultant measure is the average pain intensity in the legs and back, if applicable, experienced by the patient during the week prior the visit to the outpatient clinic. During each visit the one VAS will be completed for both legs and one VAS for back pain if applicable. The patient is not entitled to see the pain scores indicated during previous visit(s).

7.4.6 Perceived Recovery
This scale measures the perceived recovery. It is a seven-point Likert scale varying from ‘completely recovered’ to ‘worse than ever’. The scales will be completed by the patient, research nurse, and if available, the neurosurgeon.

7.4.7 Patient Global Impression of Change
This scale measures the change in the patient complaints compared to the situation before the situation. The scale will be completed by the patient, research nurse, and if available, the neurosurgeon.

7.4.8 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. 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.

7.4.9 Costs
7.4.9.1 EuroQol (EQ-5D)
The EuroQol (EQ-5D) will be used for the cost utility analysis at the end of the investigation. As indicated by the name the tool measures five dimensions:
- mobility
- self-care
- daily activities
- pain/discomfort
- anxiety/depression.
Each dimension consists of one item, while three levels are distinguished (no problems, some problems, many problems).
This tool provides the possibility to link the multidimensional description of quality of life to a valuation (or utility). This utility may be linked to the duration of the health situation in question. Together with the remaining life expectation, they form QALY’s. The QALY is a measure for the number of years that someone still may expect, corrected for their quality.

By measuring the utilities, a special form of cost effectiveness analysis comes about in which the measured measure is expressed in cost per QALY’s of one treatment compared to the other, less effective treatment. Together with the VAS, the EuroQol is an important result measure which will be established by the research nurse during each visit to the outpatient clinic on the basis of the interview. The EuroQol is an effect measure that uses the utilities of the general population and can easily be filled in at home. This contrary to the Time Trade Off and the
SG which will not be used either in this research, having the disadvantage of being complicated for most of the patients and time-consuming for the research nurse. The EuroQol will be repeated once a week during the first 8 weeks after surgery. These frequent EuroQol measurements during the first 8 weeks has been chosen in order to record well the changes in quality of life, which often occur in this period due to surgery. In this EuroQol a VAS for quality of life has also been included. Although this VAS has not yet been validated, it can be included in utilities of the general population after transformation via the formula $U = 1-(1-VAS)^a$.

7.4.9.2 Costs

Based on a questionnaire that will be completed during an interview with the patient and a diary with made costs completed by the patients insight will be obtained in the need for care, working participation and direct- and indirect medical cost. Direct medical cost will be estimated on basis of the cost centre method. Work participation or loss of production, an approach will be chosen that is a mixture between the "friction cost" and "human capital approach". In addition it is expected that the study population will consist of elderly people who may be retired. For a the cost calculation additional costs as of help in house, transport, help from family, etc will be taken in account. For an estimation of direct- and indirect costs permission of the patient will be asked to request the total amount of cost incurred during the research period from the insurance company. No consideration will be given to the specification of the cost. Additional cost incurred by participation in the investigation as compared to daily practice will be deducted. The additional investigational costs are mainly the additional visits to the outpatient clinic.

A detailed description of the cost analysis will be provided in 13.7 Cost Effectiveness.

The patient will be requested to keep a diary for the financial aspects of the consequences of INC and corresponding treatment. The patient will be requested to record the following items:
- visits to GP
- visits to physiotherapist
- visits to specialist
- alternative medicines and devices (e.g. rollator, etc)
- number of days of hospitalization
- pain medication; dosage and frequency
- illness-related days of absence at work, if any
- cost of loss of production and substitute manpower, if any,
- additional travelling expenses on account of INC
- help in householding

7.4.10 MRI, CT and X-ray

A pre-operative diagnostic MRI, CT and functional X-ray will be obtained for all patients. The MRI will be evaluated in respect with INC caused by lumbar vertebral stenosis by the (neuro)radiologist and neurosurgeon following the protocol of the relevant hospital. Other parameters that will be measured in the MRI's are:
- extent of stenosis
- area of spinal canal (mm²)
- facet hypertrophy
- ligamentum flavum
7.4.11 Complications
The neurosurgeon and research nurse will record complications accurately. This will be examined specifically in respect of:
- infections, divided into superficial wound infections and deep wound infections
- post-surgical haematoma
- an increase in neurological failure due to surgery
- venous thrombosis
- other (serious) side effects.

7.4.12 Re-operation Incidence
In numerous studies regarding vertebral column surgery repeated surgery is considered as a very poor result of the initial surgery and therefore used as effect measure. In this investigation the incidence of repeated surgery will also be used as an effect measure.

7.4.13 Operative Data
The following data of the surgery will be stated in the standard Case Report Form (CRF) form by the operating surgeon on the discharge forms:
- treated lumbar levels
- type of anaesthesia
- duration of surgery
- estimated loss of blood
- duration of hospitalization
- size of implant and lot number of Coflex™ per level, if applicable
- surgical decompression details as appropriate – laminectomy, foraminotomy, unilateral or bilateral, if applicable
- operative or post-operative complications.

7.5 Timing of Analysis
Patients will be evaluated preoperatively and postoperatively at 4, 8 weeks, 6, 12, 24 & 60 months.

8 Patient Selection

8.1 Target Population
All patients with minimally 3 months of existing INC on the basis of stenosis of the lumbar vertebral column who contact the neurologist or neurosurgeon directly will be eligible for participation in the investigation and randomisation on condition that they satisfy all inclusion- and exclusion criteria.

8.2 Inclusion Criteria
Patient will be eligible for inclusion in the investigation if he/she:
- signed informed consent
- is 45 to 80 years old at time of surgery
- has INC, as noted by leg/buttock/groin pain with or without back pain. Leg/buttock/groin pain needs to be strongly relieved when flexed such as when sitting in a chair
- has received at least three months of conservative care therapy which may have included, but is not limited to, physical therapy, bracing, systemic and/or injected medications
- has a regular indication for surgical intervention of INC
- has a narrowed lumbar spinal canal, nerve root canal or intervertebral foramen at one or two levels confirmed by MRI
- is physically and mentally willing and able to comply with, or has a caregiver who is willing and able to comply with, the post-operative evaluations.

### 8.3 Exclusion Criteria

Patient will be excluded from participation in the investigation if he/she:
- has cauda equina syndrome defined as neural compression causing neurogenic bowel (rectal incontinence) or bladder dysfunction (bladder retention or incontinence)
- has Paget’s disease, severe osteoporosis or metastasis to the vertebrae
- has significant scoliosis (Cobb angle > 25 degrees)
- has a Body Mass Index (BMI) > 40 kg/m²
- has had any surgery of the lumbar spine
- has degenerative spondylolisthesis > grade 1 (on a scale 1 to 4) at the affected level
- has significant instability of the lumbar spine
- has severe comorbid conditions that will increase the risk to the patient or interfere with the evaluable of this study
- has a fused segment at the indicated level.

### 9  DESCRIPTION OF THE DEVICE AND SURGICAL TECHNIQUES

For both group A and B surgery will be planned immediately after randomization, normally within 4 weeks. The research nurse will coordinate the planning in consultation with the outpatient clinic, nursing department, and the operating theatre coordinator, the management of the operating theatre, and the relevant neurosurgeon. In principle, the patient will be admitted to the hospital that also performed the intake and baseline procedures for this investigation. Due to capacity problems (full operation schedule, full nursing department) another participating hospital may be consulted occasionally. The patients will be admitted per routine practice.

#### 9.1 Coflex™ IPD Device

The Coflex™, a PEEK and titanium implant that fits between the spinous processes of the lumbar spine, is comprised of two components: a wing assembly and a spacer assembly.

The Coflex™ is available in six sizes: 6mm, 8mm, 10mm, 12mm, 14mm and 16 mm. The size refers to the minor diameter of the oval spacer assembly of the Coflex™.

#### 9.2 Coflex™ IPD Device - Surgical Technique

The patient lies in salaam (knee-elbow) position under general anaesthesia. Via palpation and fluoroscopy the surgery level is determined. After median incision over the processi spinosi, the laminae of the affected level(s) are exposed subperiostally. With a special instrument space will be created in the interspinal ligament between the processi spinosi of the affected level(s). Ventral of the ligamentum supraspinale a spreader is placed which will distract the segments. Based on the desired distraction the size of IPD is determined with the spreader. The Coflex™ is placed in the created space between the processi spinosi with the insertion instrumentation. If applicable, a second IPD will be placed in a similar manner at an adjoining level. If required, a
9.3 Decompression – Surgical Technique
The patient lies in face-down position or salaam position under spinal or general anaesthesia. Via palpation and fluoroscopy the surgery level is determined. A median lumbosacral incision will be made and after subperiostal shifting the muscles on will be spread unilaterally or bilaterally. The level will be identified and decompression will be applied via resection of the laminae or bilateral foraminotomy. Facet joints will be saved in order to maintain the stability of the segments. No arthrodesis will be applied. If required, a vacuum drain will be placed and the wound will be closed in layers. A post-operative X-ray will be obtained to judge the operated level.

9.4 Postoperative Care
The post-operative treatment will differ per patient’s need. The patient will be allowed to leave the bed and walk without aid at the day of surgery. If the patient regains his/her physical function, the patient will be discharged. Post-operative policy can consist of the gradual resumption of the daily activities and work, physical therapy and posture improvement will be given in accordance with ‘usual care’. The patient is allowed to fully resume the daily activities when no physical limitations are present with respect to the daily activities.

9.5 Necessary Training
Surgeons with experience of both IPD (Coflex) and also surgical decompression will be allowed to join in this study. In the case of a lack of experience with either of the two techniques surgeons must complete a learning curve of treating 5 cases prior to commencement of randomisation.

10 CLINICAL INVESTIGATION PROCEDURES

10.1 Intake (outpatient)
Recruitment Phase
Patients with INC who are referred to a neurologist or the neurosurgeon directly in one of the recruiting or hospitals in which the surgery will be performed and who, moreover, have been treated unsuccessfully for 3 months with conservative methods (such as physical therapy, medication) will be eligible for participation in this trial. The treating physician will discuss the investigation with the patient and if the patient fulfils all inclusion- and exclusion criteria, the patient will receive the patient information form and the informed consent form. The patient can read subsequently at leisure at home.
In addition an appointment will be scheduled for the usual required tests including X-ray, CT, ECG, lab assessment, etc.
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.

Visit 1
If the patient would like to participate in the investigation, an appointment with the research nurse at the outpatient clinic of the hospital will be made in the short-term.
During this visit, the patient will be extensively informed about the backgrounds, the objectives, the investigational design and the assessments of the investigation, the possible advantages and disadvantages of the investigation by the research nurse. All this information provided by the research nurse is also described in the earlier provided patient information form. To maintain the blinding of the patient the patient will be informed that hospitalization after surgery will vary from 0 to 7 days and that the post-operative procedures are depending on his/her physical condition instead of depending on the kind of surgery the patient received. If the patient would like to participate in this investigation, he/she will be requested to sign the informed consent form in presence of the research nurse. After written consent is obtained the research nurse will explain further about the data that needs to be collected, which may be in a form of loose sheets or a diary. Pre-operative baseline data will then be collected for the outcome scores as well as patient’s demography, etc. In addition a neurological examination will be performed, the MRI and other tests will be reviewed, the surgery will be discussed and the anaesthesiologist will provide information.

In the case the patient is recruited by one of the recruiting hospitals, the patient will be informed that the surgery will be performed in another hospital instead of the recruiting hospital and that all outpatient follow-up procedures will be performed in his/her local hospital by a research nurse.

The pre-inclusion diagnostic MRI will be reviewed and a report produced to indicate the status of the narrowing of the lumbar vertebral canal, nerve root canal or intervertebral foramen at maximally 2 levels. The MRI data will be completed independently by the radiologist and the surgeon.

10.2 Randomization, Surgery and Discharge (inpatient)
Visit 2
Patients who meet the inclusion- and exclusion criteria, have INC based on lumbar spinal stenosis in a maximum of two levels confirmed by MRI, have given informed consent, will be allocated the next available investigational number (Patient ID number) and will be randomly allocated to one of two groups (treatment A or treatment B) by use of sequentially numbered sealed envelopes. The envelope contains a card indicating which treatment the patient will receive.

The envelope will be opened in the operating theatre just before the surgery will be performed. Surgery forms and implant numbers shall be archived at the SIPS-LUMC. The patient will be informed which procedure was performed at 1 year after surgery.

Visit 3
After the surgery the patient will be discharged following as per routine practice. Before discharge the research nurse will perform the discharge assessment and explain and provide the diary cards, the EuroQol questionnaires and the ZCQ questionnaires which have to be completed in the coming period.

10.3 Follow-up Assessments (outpatient)
Visit, 4, 5, 6, 7 and 8
Follow-up of all patients will be performed in accordance with the flow-chart below. The neurosurgical examination after 8 weeks will be combined with a visit to the research nurse. This and following follow-up visits will be performed by the research nurse, who will review the completed patient-derived questionnaires and obtain any missing information, will record VAS pain score in legs and back through an interview and will examine the patients physically for still
present pain/irritation and/or failure in the legs. The interview will take approximately 30 minutes including a short neurological examination. At the end a copy of the questionnaire required to be completed at the next visit will be provided to the patient for visits in the first year. For follow-up visits at 2 and 5 years the patient will receive a copy of the questionnaire by post which can be completed in front of the next visit.

### 10.4 Flow chart

<table>
<thead>
<tr>
<th>Visit 1: Intake</th>
<th>Visit 2: surgery</th>
<th>Visit 3: Discharge</th>
<th>Visit 4: Follow-up 8 weeks</th>
<th>Follow-up 3 months(^a)</th>
<th>Visit 5: Follow-up 6 months</th>
<th>Visit 6: Follow-up 12 months</th>
<th>Visit 7: Follow-up 24 months</th>
<th>Visit 8: Follow-up 60 months</th>
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<tbody>
<tr>
<td>In-patient</td>
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<tr>
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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>
<td>Demography &amp; diagnosis</td>
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<td>Basic physical examination</td>
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<tr>
<td>Neurological examination</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Provide study information</td>
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<tr>
<td>Obtain informed consent</td>
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<tr>
<td>ZCQ</td>
<td>x</td>
<td></td>
<td>x(^b)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>MRDQ</td>
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<tr>
<td>Shuttle Walking Test</td>
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<tr>
<td>VAS for legs and back</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Perceived Recovery</td>
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<tr>
<td>Patient Global Impression of change</td>
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<td></td>
<td></td>
<td></td>
<td>x(^c)</td>
<td>x</td>
<td>x</td>
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<tr>
<td>EuroQol &amp; VAS Quality of Life</td>
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<td>x</td>
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<td>Patient diary</td>
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<td>x</td>
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<tr>
<td>Review MRI</td>
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<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>
</tr>
</tbody>
</table>

\(^a\) questionnaires will be sent per mail with request to complete and return them

\(^b\) at 2 and 4 weeks after surgery and then at selected time points

\(^c\) once per week for first 8 weeks after surgery and then at selected time points
11 ADVERSE EVENTS

The frequency and nature of reported adverse device events and/or relevant adverse events will form the basis of the safety evaluation of the study.

11.1 Adverse Event
An ‘adverse event’ is defined as ‘any toward medical occurrence in a patient’. This definition does not imply that there is a relationship between the adverse event and the device/procedure under investigation. An adverse event can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease temporarily associated with the use of the investigational product, whether or not related to the investigational product.

11.2 Serious Adverse Event
A ‘serious adverse event’ is defined as ‘an adverse event that:
   a) led to a death
   b) led to a serious deterioration in the health of the patient that
      1) resulted in life threatening illness or injury
      2) resulted in a permanent impairment of a body structure or a body function
      3) required in-patient hospitalization or prolongation of existing hospitalization
      4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function
   c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

11.3 Adverse Device Effect
An ‘adverse device effect’ is defined as ‘any untoward and unintended response to a medical device’. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.

11.4 Serious Adverse Device Effect
A ‘serious adverse device effect’ is defined as ‘an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune’.

11.5 Reporting of Adverse Events
In the case of an ‘adverse event’ the investigator is responsible for reporting this within 48 hours of being made aware of the event.
In the case of ‘a serious adverse event’ the investigator is responsible for reporting this within 24 hours of being made aware of the event.

All ‘adverse events’ and ‘serious adverse events’ should be reported to the study manager at SIPS-LUMC:
Christi Waanders
Clinical Research Coordinator
SIPS
Leiden University Medical Center
c.c.a.waanders@lumc.nl
The study manager shall be responsible for ensuring that all AR forms concerning product complaint problems reported for a patient will be documented as fully as possible. Where appropriate the Study Manager will notify local sales and marketing personnel of any problems with patients involved in the study.

**11.6 Device Failure**
Device failure MUST be recorded within the adverse event section of the CRF. A full explanation of the cause and treatment is required. The revised components should be kept and returned to Paradigm Spine for analysis of the problem wherever possible. Immediate prerevision x-ray films will also be required. ‘Revision Surgery’ for the purposes of this study should be considered to have taken place when any, or all, components of the implant are removed and replaced due to device failure.

**12 CLINICAL INVESTIGATION TERMINATION**

**12.1 Patient Lost to Follow-Up**
The investigator will complete and sign the appropriate CRF when a patient is lost to follow-up. The date and type of attempted communication with the patient will also be documented.

**12.2 Patient Withdrawals and Discontinuation**
Subjects will be advised that they may voluntarily withdraw from the study at any time and will be instructed to notify the investigator immediately. Subjects may choose to withdraw for any reason and will be asked their reasons for withdrawal. All information regarding the patient discontinuation in the study will be properly recorded.

A subject may be withdrawn from the clinical study for the following reasons:

a) patients may choose to withdraw from the study under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason
b) any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued
c) the development of any intercurrent illness(es), infection or condition(s) that might interfere with the CIP
d) non-compliance with the study procedures deemed by the investigator to be sufficient to cause discontinuation
e) any problem deemed by the Investigator to be sufficient to cause discontinuation.

All patients discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, will be treated until the reaction resolves.

The Investigator will clearly document the date and reason(s) for the patient withdrawal in his/her CRF and the study monitor will be informed.

Patients who have withdrawn from the study will not be replaced if they have received investigation treatment. If possible, any procedures or assessments planned for the patient on withdrawal from the investigation should be performed when intention to withdraw the patient is announced.
Patients who are withdrawn prior to receiving treatment will be replaced.

### 12.3 Early Termination of Clinical Study
Both the Investigator and LUMC reserve the right to terminate the clinical study at any time. After review of the clinical data, the sponsor and investigators will jointly make a decision to terminate the study if necessary. Should this be necessary the procedures will be arranged on an individual investigation basis after review and consultation by both parties.

Amendments and Deviations from the Study CIP must be avoided as far as possible and fully documented if they occur. The Study CIP must not be modified without the prior and written permission of Paradigm Spine.

### 13 DATA COLLECTION AND MANAGEMENT

#### 13.1 Completion of Case Report Forms
Prior to the start of the investigation, LUMC will provide the Investigator with one CRF for each patient to be enrolled at that centre. The Investigator will be responsible for the timing, accuracy and completeness of the CRF for each individual patient. However, the investigator may delegate study form completion to suitably trained members of his team. All entries are to be made in black ink. The personal data reported on all documents will be regarded as confidential.

The Investigator must record the patients’ participation in this investigation in the patients’ hospital notes. In addition, the Investigator must keep a separate patient study log maintaining relevant data, as supplied.

#### 13.2 Data Management
Data management will be the responsibility of Ronald Brand (LUMC) and data will be maintained on paper and electronically.

In all instances data will be identified as indicated in the patient informed consent documentation, in-line with explicit patient consent and in compliance with the European Data Privacy Directive (95/46/EC).

#### 13.3 Retention of Documentation
All study related documentation shall be retained for a period of minimal 5 years after the study completion or longer if deemed necessary. It is the investigator's responsibility to ensure these are filed in a secure place.

#### 13.4 Monitoring
The Investigator shall be responsible for ensuring that all data is entered onto the CRFs in a timely and accurate manner.
13.5 Sample Size
The sample size is calculation is based on the hypothesis that the results obtained with IPD (Coflex) are equivalent (non-inferior) to the results obtained with surgical decompression. The ZCQ will be used as primary result measure both to answer the phrasing of the research question and to calculate the sample size.

The sample size calculation is based on the following parameters:

- Alpha: 0.05 (2-sided)
- Beta: 0.20 (80% power)
- Success rate Coflex\textsuperscript{TM}: 50%
- Success rate surgical decompression: 50%
- Sample size ratio: 1:1
- Delta: 15%

These assumptions will yield a required sample size of 350 patients. Based on an expected drop-out rate of 10% 386 patients will be considered as a satisfactory sample size.

13.6 Treatment Success
The definition of success for the individual patient is the following:
- Clinical significant success in at least two domains of the ZCQ. For the domains physical function and symptom severity this is defined as a decrease of 0.5 points on the score of these domains compared to preoperative. For the domain patient satisfaction it is defined as a score of less than 2.5
- Patient did not require additional surgery for lumbar spinal stenosis.

13.7 Cost Effectiveness
For the cost-effectiveness analysis the following secondary effect measures will be used in particular:
- SF-36, a generic health-related quality of life questionnaire
- EuroQol

For the cost-utility analysis will be based on QALY’s which is a derivative from the secondary effect measure EuroQol.

Per patient QALY’s will be estimated based on EuroQol. The generic and disorder-specific quality scales will be measured by respectively the ZCQ, SF-36 and RDQ.

The expectation is that cost differences can traced back to differences in hospitalization period, local vs. general anaesthesia, and post-surgical recovery policy. In the cost analysis the societal calculated cost during the first five years after randomization will be estimated. The below-mentioned three cost categories will be distinguished.

Cost of hospitalization on behalf of surgery
The cost of hospitalization will be based on the integral cost price. The integral cost price will be determined on analysis of cost in participating peripheral hospitals. The centres will be aggregated pro rata of the number on which the cost analysis is based. End result of this institute analysis will be an estimated fixed cost for hospitalization and an estimated variable
cost per day of hospitalization. Combined with the period of hospitalization the individualized
cost per hospitalization for all patients can be calculated.

Other medical cost
Other medical cost is cost for visits to GP, specialist and physiotherapist, hospitalization, and
medication. This item will be an estimation based on the information recorded in the patient’s
diary that will be gone through at the measuring moments. Rates will be used as cost prices.

Non-medical cost
Additional expenses will be recorded in the diary by the patient. For an estimation of the indirect
cost, like productivity cost, days of illness-related absence will be recorded in the diary and the
research nurse will list the work situation, the work efficiency, the gross salary if applicable and
help from professionals for householding.
Based on the loss of production the Friction Cost will be used and based on the time frame of 2
years and more the Human Capital Approach will be used.
Due to the frequent medical contacts for the investigation the other medical cost are presumably
underestimated in both arms of the investigation. No attempt will be made to correct this.

For the cost-effectiveness analysis the medical and non-medical cost will be compared in a cost
minimization analysis. If no strict dominance of one of the two randomization arms is observed,
the cost and effects will be compared proportionally. In this cost-utility analysis the difference in
total cost during five years will be compared to the difference in QALY during five years (with the
utilities of the general population on the classification system of the EuroQol26,27

13.8 Statistical Methods and Analysis Plan of Outcome Scores
The investigation compares the effectiveness of surgical decompression without fusion to the
surgical IPD procedure in a randomized design. The efficiency of the treatment will be evaluated
with a “mixed model analysis of variance”.

Next to the fact that an analysis will be performed that examines the difference in the extent of
recovery between the two groups, analyses will be performed that examine the difference in time
necessary to achieve recovery. The analyses will be based on the “Intent to Treat” principle.

Subgroups will be composed beforehand based on the following variables:
- age and age banding (< 60 years, > 60 years or similar linked to groups size after
  recruitment))
- long medical history of backache
- leg pain intensity
- proportion leg pain/backache
- extent of stenosis during MRI examination
- kind of stenosis (soft or bony)
- sex
- surface area of spinal canal.

Stratified subgroups will be comparatively tested to investigate if any derive
increased/decreased benefit with the IPD (Coflex™) consists in comparison with the remaining
subgroups.

For this subgroup analysis the following hypotheses will examined:
patients with a walking distance < 50 meters will show faster recovery in case of IPD surgery than surgical decompression

patients in whom a IPD is inserted at two levels will show faster recovery than patients on whom surgical decompression has been carried out at two levels.

13.9 Management of Drop-Outs
Patients who undergo decompressive surgery at the lumbar-implanted level will be treated as failures at all time periods subsequent to implant. Patients who fail to return for other reasons will be assessed based on the Last Observation Carried Forward (LOCF) method for the ZCQ score; that is, the values from the most recent post-treatment visit will be used. Analyses excluding LOCF imputed values will also be performed and any differences between the results of the two methods will be further examined.

Safety variables, secondary efficacy variables, demographic and baseline variables will be similarly analyzed except that LOCF imputation will not be used.

13.10 CIP Deviations
This study will be conducted in compliance with the CIP, Good Clinical Practices (GCP) and/or ISO14155, and all applicable regulatory requirements associated with the Medical Device Directive. Should a CIP deviation occur, it shall be recorded together with an explanation for the deviation. CIP deviations will be reported to the Sponsor who will analyze them and assess their significance.

13.11 CIP Amendments
All amendments to the CIP shall be agreed between Sponsor and the Clinical Investigator and be recorded with a justification for the amendments. No changes to this CIP will be permitted without approval of the Sponsor. If CIP changes become necessary, written approval by the Investigator’s EC will be obtained before changes are implemented.

14 Publication of Results
Surgeons remain free to use their own data for any purpose at any time but the use of pooled data will not be allowed without the permission of all contributors.

15 Ethical Considerations
This investigation will be performed according to the following guidelines:
- Declaration of Helsinki 2004
- ISO 14155-1 & ISO 14155-2 2003
- WMO Wet medisch-wetenschappelijk onderzoek met mensen 1999
15.1 Ethics Committee Approval
Prior to the initiation of this investigation, the Investigator must submit the CIP, patient information sheet, patient consent form and any other documentation as required to the appropriate EC for review and approval. The Investigator, and any other member of the investigational 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 CIP will be requested.

15.2 Patient Information and Informed Consent
The investigator or his/her designee will inform all subjects regarding the purpose of the study, follow-up schedule, and expected duration. The investigator will discuss the foreseeable risks as well as potential benefits that may result from participating in the study.
Subjects will be informed by the investigator that they are free to refuse to participate in the study and, if they choose to participate, that they may withdraw from the study at any time without comprising further medical care. In addition, the subjects will be informed that the investigator may terminate their participation without their consent. Subjects will be informed by the investigator that their medical records will be subject to review by the sponsor’s representatives, and may be subject to review for the auditor and regulatory authorities, and that the information will be used during the analysis of the results of the clinical study but the confidentiality of subjects will be maintained at all times. Permission must also be given to store the data electronically, this will be anonymous and conform to the Data Protection Act 1998.

15.3 Patient Confidentiality
Confidentiality of patient data will be maintained at all times. Patient anonymity will be guaranteed and all documentation relating to a patient will be kept in a secure location.

15.4 Declaration of Helsinki
This study will be conducted in accordance with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964 and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington (2002) and Tokyo (2004).

There are three main areas covered by the declaration, namely:

1. Freely given informed consent should be obtained from a patient before inclusion in any study. This means that a patient has the right to know that he is being asked to take part, and that he does not have to do so unless he chooses. The patient must also understand that there will be no financial rewards if he agrees to participate.
2. The study has been reviewed by an independent EC and approved as being ethically constituted.
3. Patients should also know that if they choose not to participate or change their mind after the start of the study that this decision would not affect their medical care in the future.

15.5 Independent Physician
In any case the patient can contact the independent physician. The assigned independent physician is:
Prof. Dr. R.F. Rosendaal
Leids Universitair Medisch Centrum
the Netherlands
tel. number: 071 526 4037
15.6 Indemnity
Paradigm Spine/InSpine recognizes its liability in law to compensate for any injury sustained by patient participation in this investigation in accordance with the guidelines of the Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk onderzoek met Mensen (WMO)) for any patients entered into the investigation in the Netherlands, or other relevant guideline in existence in other European Country where the study is conducted.

15.7 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)).

16 DURATION OF INVESTIGATION

- Start date: Q4 2007
- Patient numbers: 386 in total, 193 per group
- End inclusion: Q4 2009
- End investigation: Q2 2014
17 REFERENCES

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15 Pratt RK, Fairbank JC, Virr A. The reliability of the Shuttle Walking Test, the Swiss Stenosis Questionnaire, the Oxford Spinal Stenosis Score, and Oswestry Disability Index in the assessment of patients with lumbar spinal stenosis. Spine. 2002 Jan 1;27(1):84-91
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18 APPENDICES

18.1 Declaration of Helsinki
A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for
those who will not benefit personally from the research and for those for whom
the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory
requirements for research on human subjects in their own countries as well as
applicable international requirements. No national ethical, legal or regulatory
requirement should be allowed to reduce or eliminate any of the protections for
human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health,
privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted
scientific principles, be based on a thorough knowledge of the scientific
literature, other relevant sources of information, and on adequate laboratory
and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may
affect the environment, and the welfare of animals used for research must be
respected.

13. The design and performance of each experimental procedure involving human
subjects should be clearly formulated in an experimental protocol. This protocol
should be submitted for consideration, comment, guidance, and where
appropriate, approval to a specially appointed ethical review committee, which
must be independent of the investigator, the sponsor or any other kind of undue
influence. This independent committee should be in conformity with the laws
and regulations of the country in which the research experiment is performed.
The committee has the right to monitor ongoing trials. The researcher has the
obligation to provide monitoring information to the committee, especially any
serious adverse events. The researcher should also submit to the committee,
for review, information regarding funding, sponsors, institutional affiliations,
other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical
considerations involved and should indicate that there is compliance with the
principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by
scientifically qualified persons and under the supervision of a clinically
competent medical person. The responsibility for the human subject must
always rest with a medically qualified person and never rest on the subject of
the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded
by careful assessment of predictable risks and burdens in comparison with
foreseeable benefits to the subject or to others. This does not preclude the
participation of healthy volunteers in medical research. The design of all studies
should be publicly available.

17. Physicians should abstain from engaging in research projects involving human
subjects unless they are confident that the risks involved have been adequately
assessed and can be satisfactorily managed. Physicians should cease any
investigation if the risks are found to outweigh the potential benefits or if there is
conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be
stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004

18.2 Protocol for Shuttle Walking Test
A 10-m course (one shuttle) is measured on flat ground without obstacles and is marked. A tape recorder plays the SWT prerecorded tape and the test is explained to the patient. The patient must reach the end of the walkway within a specified time dictated by a beep sounding from the tape. During the first minute of the test, beeps sound each 20 seconds, and three shuttles (30 m) are completed. During the second minute, four shuttles are completed; during the third minute five shuttles are completed; and so on up to 14 transits in 12 minutes, with a maximum total distance of 1020 m. The assessor counts the number of completed shuttles.

The test ends when the patient can no longer complete a shuttle before the next beep sounds. If the patient is within 50 cm of the end of the shuttle when the beep sounds, he or she is given the opportunity to make up the distance during the next shuttle. The result is given in meters (number of completed shuttles multiplied by 10).
18.2 CRF
18.3 Patient Information and Informed Consent Form