Clinical Investigation Plan for Post Approval 'Real Conditions of Use' Study

A 2 and 5 year comparative evaluation of clinical outcomes in the treatment of degenerative spinal stenosis with concomitant low back pain by decompression with and without additional stabilization using the coflex® Interlaminar Technology for FDA Real Conditions of Use Study.

Project Number	PAS003
Version	November 2018
Sponsor/Affiliate	Paradigm Spine 505 Park Avenue, 14th Floor New York, NY 10022
Device name	coflex® Interlaminar Technology P110008 approved October 12, 2012
Clinical Research Organization (US)	Musculoskeletal Clinical Regulatory Advisers, LLC CRO Washington, DC
Number of sites	Up to 20 (10 coflex; 10 control)
Planned Time Schedule:	
Date of Study Initiation	July 2015
Monthly Number of Study Sites with IRB Approvals	1-2
Start of Recruitment	September 2016
Expected Subjects Enrolled per Month	Approximately 15 Subjects
Planned End of Recruitment	September 2020
Completion of Month 24 Follow-Up	September 2022
Completion of Month 60 Follow-Up	September 2025
Planned Draft Interim Report	December 2022
Planned Draft Final Report	December 2025

SIGNATURE PAGE

This clinical investigation plan was subject to a critical review and has been approved by the appropriate review committee of *Paradigm Spine*. The information it contains is consistent with:

- The current risk/benefit evaluation of the device preparation;
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki in its current version as well as the EN ISO 14155-1 and -2;
- Good clinical practice guidelines as applicable for medical devices in their current version, and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA
- supervise all testing of the device involving human subjects, and
- Ensure that the requirements for obtaining informed consent are met.

Paradigm Spine

.....	.....
(Place, date)	*(Marc Viscogliosi* *CEO Paradigm Spine)*

All further investigators have to give their agreement with the content of this CIP on a separate "signature page to clinical investigational plan".

TABLE OF CONTENTS

Page

SYNOPSIS OF THE CLINICAL INVESTIGATION PLAN

SPONSOR **NAME OF STUDY PRODUCT**	Paradigm Spine LLC coflex® Interlaminar Technology
Class of Medical Device	Class III
STUDY TITLE	A 2 and 5 year comparative evaluation of clinical outcomes in the treatment of degenerative spinal stenosis with concomitant low back pain by decompression with and without additional stabilization using the coflex® Interlaminar Technology for FDA Real Conditions of Use Study.
INT. PROJECT NUMBER	PAS003
PROJECT MANAGER	TBD
CRO	Musculoskeletal Clinical Regulatory Advisers, LLC CRO Washington, DC
PRINCIPAL INVESTIGATOR and RELATED STUDY SITE	TBD
FURTHER INVESTIGATORS and RELATED STUDY SITES	TBD
RELEVANT LITERATURE	Stucki, Gerald, MD. et al., Measurement Properties of a Self-Administered Outcome Measure in Lumbar Spinal Stenosis. Spine. Vol. 21(7). pp. 796-803.[8] Pratt RK, MA, FRCS, et al. The Reliability of the Shuttle Walking Test, the Swiss Spinal Stenosis Questionnaire, the Oxford Spinal Stenosis Score and the Oswestry Disability Index in the Assessment of Patients with Lumbar Spinal Stenosis. Spine Vol. 27 (1) pp. 84-91.[7] Fairbank J.C.T., The Oswestry Disability Index, Spine Volume 25, Number 22, pp 2940–2953, 2000[11]
DURATION OF THE CLINICAL INVESTIGATION	Per Patient: 60 months Recruitment 36 months Total: 96 months
OBJECTIVES	Meet FDA mandated post-approval Real Conditions of Use evaluation

METHODOLOGY and STUDY DESIGN	Prospective, multicenter, concurrently enrolled, propensity score controlled through Month 60. Up to 10 treatment (coflex) sites Up to 10 control (decompression) sites
NUMBER OF PATIENTS	150 per group (300 total) plus 15% to account for LTF in both; plus 20% in control group and 5% in the study device group to account for trimming of control patients and possible trimming of study device patients during the propensity score design. Therefore, the total enrolled will be 186 coflex patients and 220 decompression control patients.
DIAGNOSIS and INCLUSION CRITERIA	1. Radiographic confirmation of at least moderate lumbar stenosis, which narrows the central spinal canal at one or two contiguous levels from L1-L5 that require surgical decompression. Moderate stenosis is defined as > 25% reduction of the antero-posterior dimension compared to the next adjacent normal level, with nerve root crowding compared to the normal level, as determined by the investigator on CT Scan or MRI.* The patient may have, but is not required to have for inclusion in the study: (a) Facet hypertrophy and subarticular recess stenosis at the affected level(s); (b) Foraminal stenosis at the affected level(s); (c) Up to stable Grade I degenerative spondylolisthesis (Meyerding classification) or equivalent retrolisthesis as determined by flexion/extension X ray: i) For single level disease, there may be up to a stable Grade I spondylolisthesis or equivalent retrolisthesis at the affected level as determined on flexion/extension films by the investigator. ii) For two level disease, there may be up to a stable Grade I spondylolisthesis or equivalent retrolisthesis at <u>only one</u> of the two contiguous affected levels as determined on flexion/extension films by the investigator. Patients with up to stable Grade I spondylolisthesis at two contiguous levels are excluded, but patients with up to Grade I stable spondylolisthesis at one level and equivalent retrolisthesis at the adjacent level may be included. (d) Mild lumbar scoliosis (Cobb angle up to 25º) 2. Radiographic confirmation of no angular or translatory instability of the spine (instability as defined by White & Panjabi: Sagittal plane translation >4.5mm or 15% or sagittal plane rotation >15° at L1-L2, L2-L3, and L3-L4;

	>20° at L4-L5 based on standing flexion/extension X-rays) 3. VAS back pain score of at least 50 mm on a 100 mm scale. 4. Neurogenic claudication as defined by leg/buttocks or groin pain that can be relieved by flexion such as sitting in a chair. 5. Patient has undergone at least one epidural injection at any prior time point, AND at least 6 months of prior conservative care without adequate and sustained symptom relief. 6. Skeletally mature. 7. Oswestry Low Back Pain Disability Questionnaire score of at least 20/50 (40%). 8. Appropriate candidate for treatment using posterior surgical approach. 9. Psychosocially, mentally, and physically able to fully comply with this protocol, including adhering to scheduled visits, treatment plan, completing forms, and other study procedures. 10. Personally signed and dated informed consent document prior to any study-related procedures indicating that the patient has been informed of all pertinent aspects of the trial. *The Lumbar Spine (H. Herkowitz ed. 2004, Lippincott Williams, & Wilkins).
EXCLUSION CRITERIA	1. More than two contiguous vertebral levels requiring surgical decompression. 2. Prior surgical procedure that resulted in translatory instability of the lumbar spine [as defined by White & Panjabi (see Inclusion Criteria, Item #2)]. 3. More than one surgical procedure at any combination of lumbar levels. 4. Prior fusion, implantation of a total disc replacement, complete laminectomy, or implantation of an interspinous process device at index level. 5. Radiographically compromised vertebral bodies at any lumbar level(s) caused by current or past trauma or tumor (e.g., compression fracture). 6. Severe facet hypertrophy that requires extensive bone removal which would cause instability. 7. Isthmic spondylolisthesis or spondylolysis (pars fracture). 8. Degenerative lumbar scoliosis (Cobb angle of greater than 25°).

	9. Disc herniation at any lumbar level requiring surgical intervention. 10. Osteopenia: A screening questionnaire for osteopenia, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients who require a DEXA bone mineral density measurement. If DEXA is required*, exclusion will be defined as a DEXA bone density measured T score of ≤ -1.0 (The World Health Organization definition of osteopenia). 11. Back or leg pain of unknown etiology. 12. Axial back pain only, with no leg, buttock, or groin pain. 13. Morbid obesity defined as a body mass index > 40. 14. Pregnant or interested in becoming pregnant in the next three years. 15. Known allergy to titanium, titanium alloys, or MR contrast agents. 16. Active or chronic infection – systemic or local. 17. Chronically taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids), not including a medrol dose pack. 18. History of significant peripheral neuropathy. 19. Significant peripheral vascular disease (e.g., with diminished dorsalis pedis or posterior tibial pulses). 20. Unremitting back pain in any position. 21. Uncontrolled diabetes. 22. Known history of Paget's disease, osteomalacia, or any other metabolic bone disease (excluding osteopenia, which is addressed above). 23. Cauda equina syndrome, defined as neural compression causing neurogenic bowel (rectal incontinence) or bladder (bladder retention or incontinence) dysfunction. 24. Fixed and complete motor, sensory, or reflex deficit. 25. Rheumatoid arthritis or other autoimmune diseases. 26. Known or documented history of communicable disease, including AIDS, HIV, active Hepatitis 27. Active malignancy: a patient with a history of any invasive malignancy (except nonmelanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least five years. Patients with a primary bony tumor are excluded as well. 28. Prisoner or ward of the state. 29. Subject has a history of substance abuse (e.g., recreational drugs, narcotics, or alcohol). 30. Subject is currently involved in a study of another investigational product for similar purpose.

	31. Currently seeking or receiving workman's compensation. 32. In active spinal litigation. *Primary location for DEXA scan should be the spine. In the event that the spine T score is in the osteopenic range (-1.0 to -2.5) then a T-Score from the hip may be obtained. If the T-Score from the hip comes back above -1.0 then, at the discretion of the investigator, the patient may be considered for inclusion in the study. Also, a hip DEXA may be used in the event that a spine DEXA cannot be obtained.
INVESTIGATIONAL DEVICE; DOSE and MODE OF APPLICATION	The coflex® Interlaminar Technology is an FDA approved medical device (P110008) already being marketed in the USA. The coflex® Interlaminar Technology obtained marketing approval in the US on October 17, 2012. The device will be implanted as described in the product brochure (see appendix to this CIP) after surgical decompression in patients with spinal stenosis.
TREATMENT GROUPS	Group A: decompression surgery without any further stabilization by an implant (control group) Group B: decompression surgery with additional stabilization with the coflex® Interlaminar Technology (treatment group)
OBJECTIVES	**Objective 1:** To test the hypothesis that the coflex® device in conjunction with surgical decompression is superior to decompression alone at five years based on Month 60 Clinical Composite Success (CCS). Sensitivity Analysis (Objective 1B): To test the hypothesis that the coflex® device in conjunction with surgical decompression is superior to decompression alone at five years using an alternative definition proposed by FDA to define treatment failures due to epidurals at any time **Objective 2:** To compare clinical status of patients implanted with the coflex® device in conjunction with surgical decompression relative to surgical decompression alone at two years post operatively by confirming clinical non-inferiority in terms of Month 24 composite clinical success (CCS) defined similarly to the IDE study endpoint. **Objective 3:** If non-inferiority is shown at two-years, to evaluate evidence supporting superiority at two-years in terms of Month 24 CCS. **Objective 4:** To evaluate coflex® device performance in a "real conditions of use" study by testing the hypothesis that device performance is not clinically inferior at Month 24 in

	the PAS population relative to device performance defined by IDE study results.
CRITERIA for EVALUATION: **1. EFFECTIVENESS**	**Objective 1: Month 60 Composite Clinical Success (CCS)** A similar CCS endpoint as was used in the IDE will be used to compare clinical status of patients implanted with the coflex® device relative to surgical decompression at 60 months. Month 60 success for this comparison will require the following items: ❖ At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100). ❖ No reoperations, revisions, removals, or supplemental fixation at the index level(s); ❖ No ≥2 injections or series of injections for any lumbar level**, or nerve block procedures performed to treat spinal stenosis at any lumbar level(s); or a single injection within 12 months of the 5 year endpoint. **A series of injections is considered 2-3 injections performed between 24-hour and one week intervals designed to treat a single pain event. Secondary injections performed due to patient demand or recurrence of symptoms following the initial injection are considered separate injections and would constitute a study failure. Additional details, justification, and sensitivity analyses are described in the main protocol text below. **<u>Objectives 2 and 3: Month 24 CCS</u>** For the comparison to decompression, the Month 24 CCS will be slightly modified to include any surgical intervention at index level(s). This is because the decompression only group receives no device. In summary, when comparing coflex® in conjunction with decompression to decompression alone, Month 24 CCS will require: • No "Treatment Failure" on or before the exact 2-year anniversary of the index surgery. Treatment Failure will include: 1. No surgical intervention at the index level 2. No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level • At least a 15-point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100). • No major device-related adverse event defined as an event simultaneously both 'Serious' and 'Definitely' on or

	before the exact surgical two-year anniversary. In the decompression alone group, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery. **Note:** The IDE study defined this CCS component as severe and definitely-related. This has been changed to serious and definite for consistency with other spine studies for Objectives 2 and 3 only. **Objective 4: Month 24 CCS** The identical Month 24 CCS endpoint defined for the IDE study will be used to compare PAS results to IDE study results. These results will be used to update the Bayesian posterior probabilities of non-inferiority and superiority relative to fusion that are summarized in the coflex® SSED. **Secondary Criteria:** • ODI change compared to baseline at 24 and 60 months as a continuous variables and in terms of achieving at least a 15 point improvement. • Change in Visual Analog Scale (VAS) for low back pain (on the 100 mm scale) after 24 and 60 months compared to baseline as a continuous variables and in terms of achieving a 20 point improvement. • Change in leg pain using a Visual Analog Scale (VAS) 100 mm scale after 24 and 60 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement. • Change in worst leg pain using Visual Analog Scale (VAS) 100 mm scale after 24 and 60 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement • Change of Zurich Claudication Questionnaire (ZCQ) after 24 and 60 months compared to baseline: 1. Symptom severity (range 1-5) 2. Physical function (range 1-4) 3. Patient satisfaction (range 1-4, no baseline) 4. ZCQ Overall Success (≥2 of 3 of the following) 1) Improvement in symptom severity ≥0.5 2) Improvement in physical function ≥0.5 3) Satisfied or somewhat satisfied as defined by a score of ≤ 2.5 points on the patient satisfaction domain. 5. ZCQ Overall Success components • Maintenance or improvement in EQ-5D compared to baseline

	• Change from baseline to Month 24 and Month 60 in maximum walking time from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes. • Change from baseline to Month 24 and Month 60 in time to symptoms from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes. • Neurological status (motor, sensory, reflex, SLR - assessment of maintenance of improvement after surgery throughout study duration). • Radiography Endpoints 1. Assessment of significant migration of the implant or the complete expulsion (significant is defined > 5 mm). 2. Assessment of spinous process fracture. 3. Assessment of maintenance of foraminal height 4. Assessment of adjacent level disease determined by independent radiographic review • Correlation of foraminal height changes to improvement of walking distance on a treadmill (after 24 and 60 months compared to baseline). • The CCS will be modified to examine the effect narcotics use (opioids and/or opiates) has on treatment success rates. When comparing coflex® in conjunction with decompression to decompression alone, this modified Month 24 CCS will include: • No “Treatment Failure” on or before the exact 2-year anniversary of the index surgery. Treatment Failure will include: 1. No surgical intervention at the index level 2. No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level • No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 18 that do not resolve by Month 24. • No major device-related adverse event defined as an event simultaneously both ‘Serious” and 'Definitely' according to independent Clinical Events Committee (CEC) related to the implant on or before the exact surgical two-year anniversary or exact five-year anniversary. In the decompression alone group, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery.

	Alternative CCS using treadmill test: An alternative CCS will be assessed as a secondary endpoint for Objectives 1, 2, and 3. For this modified CCS, the criterion that the Oswestry Disability Index (ODI) must improve by at least 15 points will be replaced by a criterion that more directly measures physical function. This endpoint (CCS-WDT) is a function of the maximum time a patient can walk on a treadmill (up to 15 minutes) before symptoms are too severe to continue. The specific treadmill success criterion will be an improvement in the total walking time from baseline to Month 24 of at least 8 minutes. For patients with a baseline value that is >7 minutes, the Month 24 walking test success criteria is the ability to achieve the maximum walking test time of 15 minutes. This allows patients with baseline values >7 min to be able to numerically meet this success criterion.
CRITERIA for EVALUATION: **2. SAFETY**	Documentation of Adverse Events and SAEs and implant related adverse events (e.g., breaking of implants). Specific AEs will be summarized according to incidence (per patient) and counts of AE over time. Assessment of revisions and additional stabilizations. Assessment of epidurals. Assessment of narcotics usage.
STATISTICAL METHODS	**Accounting for non randomized treatment group comparisons.** This study design includes concurrently enrolled, but non-randomized investigational and control arms. Covariate balance will be acheived through the use of sub classification based on propensity score (PS) quintiles. The PS subclasses will be determined by an outcomes blinded statistician soon after prospective enrollment is completed and before most if not all patients are evaluable for the two-year effectiveness endpoint. The process of assigning patients to subclasses will be submitted to FDA for review and acceptance prior to unblinding of the PS statistician. Selection into a PS subclass is the observational study equivalent to randomization. Subclasses will be determined using methods designed to insure that within subclass, groups are well balanced with regard to a rich clinically relevent set of baseline covariates. Analyses will proceed as if patients were randomized to treatment group within subclass and effectiveness outcomes will be compared between groups using methods that account for PS subclass. To make use of the beta-binomial updating from prior to posterior it is necessary to have a count of the numbers of successes and failures observed in the prospective trial for both groups. These are added to prior beta distribution parameters that reflect (what amounts to) the prior numbers of success and failures. Combined, these sums of successes and failures determine the Bayesian

	posterior distribution. This simplicity owes to the use of a so-called 'conjugate' prior distribution. To adjust for PS subclass, the average success rate over the 5 subclasses will be computed for each treatment group. This is to allow each quintile subclass to contribute equally to the estimated success rates. Consequently, covariate balance is preserved in the final estimates of CCS probabilities. Additional details and justification for this approach including missing data strategies are provided below. **Objective 1: (5-year superiority)** This objective is to test the hypothesis that the coflex® device in conjunction with surgical decompression is superior to decompression alone at five years. This objective will be met by testing the following superiority hypotheses: **Ho: $CCS_{coflex+decomp.} - CCS_{decomp} \leq 0$ (not superior)** **Ha: $CCS_{coflex+decomp.} - CCS_{decomp} > 0$ (superior)** An informative prior based on IDE study results for the coflex® group will be used. A non-informative will be used for decompression alone. The Bayesian posterior probability that ($CCS_{coflex+decomp.} - CCS_{decomp}$) **> 0** will be determined**. If the posterior probability is ≥ 0.95, superiority will be concluded.** **Objective 2: (2-year non-inferiority)** This objective is to compare clinical status of patients implanted with the coflex® device in conjunction with surgical decompression relative to surgical decompression alone at two years post operatively by confirming clinical non-inferiority in terms of Month 24 composite clinical success (CCS) defined similarly to the IDE study endpoint. To meet this objective, the following hypotheses will be tested: **Ho: $CCS_{coflex+decomp.} - CCS_{decomp} \leq -0.10$ (inferior)** **Ha: $CCS_{coflex+decomp.} - CCS_{decomp} > -0.10$ (not inferior)** These hypotheses will be tested by evaluating the Bayesian posterior probability that the treatment group difference in the likelihood of achieving Month 24 CCS is larger than -0.10, i.e., that the probability of achieving Month 24 CCS for patients implanted with coflex® is no more than 0.10 less than for decompression alone. The IDE Study results will form the basis of an informative prior distribution for the likelihood of success in the group implanted with coflex®. A non-informative will be used for decompression alone. Non-inferiority will be concluded if the posterior probability is at least equal to 0.95. **Objective 3: (2-year superiority)** If non-inferiority is demonstrated, then the evidence supporting superiority at two-years will be evaluated. This will be done by determining the Bayesian posterior probability that (**$CCS_{coflex+decomp.}$ –**

	$\mathbf{CCS_{decomp}}$) > 0. Superiority will be concluded if the posterior probability is at least equal to 0.95. **Objective 4: (real conditions of use):** The following hypotheses will be tested in order to evaluate whether or not coflex® device performance is clinically inferior in the PAS population compared to the IDE population using a non-inferiority δ=-0.1175. The following hypotheses will be tested. **Ho: $CCS_{PAS} \leq CCS_{IDE} - 0.1175$** **Ha: $CCS_{PAS} > CCS_{IDE} - 0.1175$.** Non-inferiority of coflex performance in the PAS populaton will be concluded if the posterior probability that (**$CCS_{PAS} > CCS_{IDE} -$** 0.1175) is at least 0.95. **Sample Size Analysis** Details concerning the Bayesian simulations for this study were previously reviewed and are included in ***Bayesian Simulations Memo, Version 4.1, May 5, 2015***. **Objective 1: (5-year superiority)** These Simulations were used to evaluate the power and type 1 error for determining superiority of coflex® in conjunction with surgical decompression relative to surgical decompression alone at Month 60. For the purpose of these simulations it was assumed that the Month 60 success rate would be 0.57 for coflex®. A posterior probability threshold of at least 0.95 was selected. Power was found to be equal to 83% if the true superiority margin is 12.5%. If the true superiority margin is only 10%, then power to conclude superiority is reduced to 65%. Type 1 error was determined through simulation by assuming that the probabilities of Month 60 success were equal to 0.57 for both device groups. The estimated type 1 error rate is equal to 0.037(SD=0.0011) based on an average of 10 identical simulations with varying randomization seeds. **Objective 2: (2-year non-inferiority)** Bayesian simulations were performed to evaluate the operating characteristics for testing the Objective 1 hypothesis non-inferiority hypothesis. In the pivotal IDE study, 135 of 204 patients (66.2%) achieved Month 24 CCS. These results were used to define the prior distribution for coflex in conjunction with surgical decompression as beta (135.5, 69.5) since the distribution prior to the IDE trial was specified as beta (0.5, 0.5). This Jeffries non-informative prior was assumed for patients undergoing decompression alone. A non-inferiority margin of -0.10 is specified. Non-inferiority will be concluded if the Bayesian posterior probability that (**$CCS_{coflex+decomp.} - CCS_{decomp}) > -0.10$** is at least equal to 0.95. When evaluating

	statistical power, it was assumed that the true success rate 0.662 for patients treated with coflex®. However, preliminary results from the German decompression study suggest some an advantage of coflex® over decompression alone. Therefore, when evaluating power, Month 24 CCS for decompression alone was assumed to be at least 2% lower, or 0.642. In contrast, Type 1 error was evaluated by assuming that the coflex® success rate was 0.662 but that the success rate for decompression was 0.10 larger. With N=150 patients per group, power was shown to be 89%; and type 1 error was shown to be 0.042 and 0.052 'prior to the prior' and with the prior engaged, respectively. **Objective 3: (two-year superiority)** Superiority will be evaluated by determining the Bayesian posterior probability that (**$CCS_{coflex+decomp.}$ – CCS_{decomp}) > 0.** Ho will be rejected in favor of Ha if the Bayesian posterior probability is at least equal to 0.95. The same prior distributions that will be used in Objective 2 will be used in the evaluation this posterior probability. The expected device group difference in Month 24 CCS between coflex® and decompression alone was evaluated based on results from an administrative analysis of the ongoing PAS being conducted in Germany. The device group difference in Month 24 overall success was 12.5% (95% CI -3.5% to 28.4%) based on a simplified CCS that incorporated reoperations, lumber injections, and ODI improvements. Bayesian simulations demonstrate that when assuming the same superiority, with N=150 patients per group will result in 88% statistical power to demonstrate superiority. Type 1 error is controlled at <0.05 'prior to prior' and with prior for coflex® engaged. If the true difference is only 10%, then power is reduced to 73%. **Objective 4: (real conditions use)** A design was identified that uses a non-inferiority margin of -0.1175 and a 0.95 posterior probability threshold. This design has an estimated type 1 error that of 0.045 and power of about 80%. Other assumptions include expected success rates 0.662 in both groups when determining power. **Other Methods:** An alternative composite endpoint will be evaluated that replaces improvements in ODI with improvements in a walking treadmill test. Secondary continuous effectiveness endpoints will be summarized by treatment group over time and as changes over time with descriptive statistics including means, standard deviations, median, minimum and maximum values. Standardized effect sizes (i.e., standardized mean differences) will be computed to facilitate comparisons across measures. Secondary categorical

	effectiveness endpoints will be summarized by treatment group over time using counts and percentages. Adverse event rates will be summarized by type of AE and for specific AE per patient using counts and percentages; and by event, summarizing event counts by visit interval over time. Device and procedure related events will be summarized by severity. Events listings will be provided that include details such as relatedness, severity, onset and resolution status will be provided for all events and for relevant subsets of events such as serious events and related events.

CLINICAL INVESTIGATION PLAN

1. Background Information

The treatment of degenerative spinal stenosis is not adequately appreciated in the literature and prospective controlled clinical studies are lacking.

Non-controlled, retrospective studies have shown very different and inhomogeneous results and allow only limited conclusions regarding clinically occurring lower back pain.

Caputy et al. (1992)[1] found in a five-year follow-up period after decompression (n=88) 27% failures, that showed recurrent neurologies and persisting low back pain. Katz et al. (1996)[2] found in a 7-10 years follow-up period (n=88) 20 patients that had to undergo further surgery. 33% complained about severe back pain and 53% showed a severe limitation of walking distance. A large study in Finland with 438 patients could show retrospectively that 38% of the patients evaluated the result of the surgery after decompression as bad or very bad (Airaksinen et al. 1997).[3] Iguchi[4] published in 2000 a series of 37 patients that were all treated surgically more than10 years earlier. It could be shown that low back pain was clearly harder to treat than leg pain or walking distance. 44% of the patients evaluated the result as only acceptable to bad.

Until now no guidelines for therapeutic treatment are defined. With isolated decompression the main neurological findings are treated. Accompanying back pain is comparably harder to treat.

The coflex® Interlaminar Technology - manufactured by Paradigm Spine - is intended for use as a permanent implant between the lamina of 1 or 2 lumbar motion segments in the treatment of moderate to severe lumbar spinal stenosis. The device is specifically designed to provide stabilization without fusion in cases of stenosis with or without facet joint hypertrophy, subarticular recess stenosis or foraminal stenosis. It is restricted for use to one or two levels in the region of L1 – L5.

The height of the neuroforamen is maintained and the facet joints will be relieved. By this a further destruction is prevented. Unlike conventional stabilization methods as for example spinal fusion, the function of the segment will be maintained and adjacent structures will be effectively protected. Possible risks, which could occur after implantation of the coflex® Interlaminar Technology are breakage of the implant, displacement of the implant, pain which is caused by the implant, infections, bleedings and hematoma. The benefit of the study lies in the fact that first-time prospective data is raised for potential improvement regarding therapy of lumbar back pain with the treatment of the lumbar spinal stenosis, which, in the future, can lead to an improvement of the therapy.

---

1 Caputy AJ, Luessenhop AJ., Long-term evaluation of decompressive surgery for degenerative lumbar stenosis, J Neurosurg. 1992 Jun;78(6):1010-1.

2 Katz JN et al., Seven- to 10-year Outcome of Decompressive Surgery for Degenerative Lumbar Spinal Stenosis, Spine: Volume 21(1) 1 January 1996 pp 92-97

3 Airaksinen O et al, Surgical outcome of 438 patients treated surgically for lumbar spinal stenosis, Spine 22(19) 1997, pp2278 – 2282

4 Iguchi T et al., Minimum 10-Year Outcome of Decompressive Laminectomy for Degenerative Lumbar Spinal Stenosis, SPINE Volume 25, Number 14, pp 1754–1759

For further details, including indications, contraindications and associated risks please see the Product Brochure and instructions for use in the appendix of this document.

2. Rationale

The coflex® Interlaminar Technology has been in clinical use for more than 10 years and is CE-certified according to the standards. Prior to US approval, only isolated, retrospective data for the clinical success is available (Samani 2000[5], Kaech et al. 2002[6])

In a clinical study to support US market approval, three hundred twenty-two randomized patients (215 coflex® and 107 fusions) from 21 sites in the United States were enrolled between 2006-2008. Subjects received laminectomy and coflex® interlaminar stabilization or laminectomy and posterolateral spinal fusion with spinal instrumentation in a 2:1 ratio. Overall device success required a 15-point reduction in ODI, no reoperations, no major device-related adverse events, and no post-operative epidural injections.

In this study, coflex® patients experienced significantly ($p<0.0001$) shorter operative times (mean 98 min vs 153 min), less blood loss (mean 110 cc vs 349 cc), and length of stay (mean 1.9 vs 3.2 days). Among patients with no Treatment Failure (no reop and no lumbar injection), there was a trend towards significantly better improvement in mean ODI scores in the coflex® cohort compared to fusion (Month 24 mean 22.0 vs 26.7, $p=0.075$). Both groups demonstrated significant improvement from baseline in all VAS Back and Leg parameters. Among non-Treatment Failures, coflex® patients experienced greater SF-12 Physical Health outcomes ($p=0.050$) and equivalent Mental Health outcomes. coflex® subjects experienced better Month 24 ZCQ outcomes compared with fusion (Symptom Severity ($p=0.023$); Physical Function ($p=0.008$); Satisfaction ($p=0.006$)).

Most importantly, 66.2% of coflex® and 57.7% of fusions achieved the FDA Month 24 composite clinical success (CCS-IDE) criterion. Based on these pivotal IDE trial results, the Bayesian posterior probability that coflex® is clinically non-inferior to fusion (delta=-0.10) at Month 24 was determined to be >0.999 using non-informative Jeffries prior distributions for both treatment groups. Similarly, the Bayesian posterior probability of coflex® superiority relative to fusion at Month 24 was 0.928. The overall adverse event rate was similar between the groups. At 2 years fusions exhibited significantly increased angulation ($p=0.002$) and a trend towards increased translation ($p=0.083$) at the superior adjacent level, while coflex® maintained normal operative and adjacent level motion. With this data, the FDA determined coflex® interlaminar stabilization to be a safe and efficacious alternative, with certain advantages over lumbar spinal fusion in the treatment of spinal stenosis and low-grade spondylolisthesis.

This randomized multicenter study generated the following peer-reviewed publications:

- Decompression and coflex interlaminar stabilization compared to decompression and instrumented spinal fusion for spinal stenosis and low-grade degenerative spondylolisthesis: Two-year results from the prospective, randomized, multicenter food and drug administration investigational device exemption trial. Davis RJ, Errico TJ, Bae H, Auerbach JD. Spine (Phila Pa 1976) 38(18): 1529-1539, 2013.

5 Samani J, Study of a semi rigid interspinous “U” fixation system, 106 patients over six years, Spinal surgery, Child Orthopaedics, 1707, 2000

6 Kaech DL et al., The interspinous “U”: new restabilization device for the lumbar spine, Spinal Restabilization Procedures, Chapter 30, 355 – 362, 2002, Elsevier Science

- Can low-grade spondylolisthesis be effectively treated by either coflex interlaminar stabilization or laminectomy and posterior spinal fusion? Two-year clinical and radiographic results from the randomized, prospective, multicenter US investigational device exemption trial. Davis RJ, Auerbach JD, Bae H, Errico TJ. J Neurosurgery Spine 19(2): 174-184, 2013.
- Mitigating adverse event reporting bias in spine surgery. Auerbach JD, McGowan KB, Halevi M, Gerling MC, Sharan AD, Whang PG, Maislin G. The Journal of Bone and Joint Surgery 95(16): 1450-1456, 2013.
- Determination of the in-vivo posterior loading environment of the coflex interlaminarinterspinous implant. Trautwein FT, Lowery GL, Wharton ND, Hipp JA, Chomiak RJ. The Spine Journal 10(3): 244-251, 2010.

3. Study Objectives and Endpoints

3.1. Study Objectives

Objective 1:
The first objective of this trial is to evaluate 5-year clinical status of patients implanted with the coflex® device in conjunction with surgical decompression relative to decompression alone. This objective will be accomplished by a Bayesian test of superiority using Month 60 composite clinical success. The composite primary endpoint for this objective is in three parts:

1. At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100);
2. No reoperations, revisions, removals, or supplemental fixation at the index level(s);
3. No ≥2 injections or series of injections for any lumbar level**, or nerve block procedures performed to treat spinal stenosis at any lumbar level(s) or a single injection within 12 months of the 5 year endpoint.

   ** A series of injections is considered 2-3 injections performed between 24-hour and one week intervals designed to treat a single pain event. Secondary injections performed due to patient demand or recurrence of symptoms following the initial injection are considered separate injections and would constitute a study failure.

Additionally, a sensitivity analysis will be performed with the condition where lumbar injections occurring at any time between surgery and Month 60 will be considered a treatment failure.

A lumbar injection is defined as any deep injection into the spine, typically under image-guidance, of steroids and/or other pharmacologic agents (e.g., facet injections or epidural injections by the transforaminal, interlaminar, or caudal routes). Other types of injections are not treatment failures such as trigger point injections, intramuscular injection for systemic administration of steroids, dry-needling, prolotherapy, or acupuncture, but a sensitivity analysis will be performed including all types of injections.

Objective 2:
The second objective of this study is to compare clinical status of patients implanted with the coflex® device in conjunction with surgical decompression relative to surgical decompression alone at two years post operatively by confirming clinical non-inferiority in terms of Month 24 composite clinical success (CCS) defined similarly to the IDE study endpoint. This objective will be achieved by conducting a Bayesian test of the null hypothesis that the probability of achieving

Month 24 CCS among patients implanted with the coflex® device in conjunction with surgical decompression is no more than 10% smaller than that for patients undergoing surgical decompression alone. An informative prior distribution for the coflex® group was formulated on the basis of results contained in the coflex® SSED.

For the comparison to decompression, the Month 24 CCS will be slightly modified to include any surgical intervention at index level(s). This is because the decompression only group receives no device. In summary, when comparing coflex® in conjunction with decompression to decompression alone, Month 24 CCS will require:

- No "Treatment Failure" on or before the exact 2-year anniversary of the index surgery. Treatment Failure will include:
  1. No surgical intervention at the index level
  2. No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level
- At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100).
- No major device-related adverse event defined as an event simultaneously both 'Serious' and 'Definitely' on or before the exact surgical two-year anniversary or exact five-year anniversary. In the decompression alone group, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery.

  Note: The IDE study defined this CCS component as severe and definitely-related and not as serious and definitely-related. This has been changed to serious and definitely related for consistency with other spine studies for Objectives 2 and 3 only.

Objective 3:
If non-inferiority is shown at two-years, to evaluate evidence supporting superiority at two-years in terms of Month 24 CCS using the same informative prior distribution for the coflex group.

Objective 4:
The fourth objective of this trial is to evaluate coflex® device performance in a 'real conditions of use' study and to confirm that coflex® device performance is not clinically inferior in the PAS population compared to the pivotal IDE trial population. The same Month 24 composite clinical success (CCS) endpoint used in the IDE trial will be used in these analyses to facilitate this comparison. If non-inferiority is concluded, the PAS results will be used to update the Bayesian posterior probabilities of that were determined in the IDE trial and documented in the coflex® SSED. The Bayesian posterior probabilities of non-inferiority and superiority relative to the fusion control at the end of the coflex® IDE trial were 0.999362 and 0.927550, respectively. These probabilities will be updated using the new coflex® enrollments into this PAS.

3.2. Primary Endpoints

The identical Month 24 CCS endpoint as was used in the IDE will be used to compare PAS results to IDE study results, and to update the Bayesian posterior probabilities of non-inferiority and superiority relative to fusion. This CCS definition requires no Treatment Failure (i.e., no reoperation, revision, replacement, or supplemental fixation at the index level(s) and no epidural injection at any lumbar level); an ODI improvement ≥ 15; as well as no new or worsening, persistent neurological deficit; and no major device-related adverse event defined as severe and definitely-related

The CCS endpoints using in Objective 2 and 3 replace severe device-related AEs with serious devide-related AEs for greater consistency with other spine studies. The relationship will be evaluated relative to the device and the surgical procedure since controls receive no device. For comparison to decompression alone, any surgical intervention at the index site will imply clinical failure.

Month 60 success for this comparison will require the following items:

- At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100).
- No reoperations, revisions, removals, or supplemental fixation at the index level(s);
- No ≥2 injections or series of injections for any lumbar level**, or nerve block procedures performed to treat spinal stenosis at any lumbar level(s); or a single injection within 12 months of the 5 year endpoint.

  **A series of injections is considered 2-3 injections performed between 24-hour and one week intervals designed to treat a single pain event. Secondary injections performed due to patient demand or recurrence of symptoms following the initial injection are considered separate injections and would constitute a study failure.

3.2.1. Discussion about Month 60 Composite Clinical Success (CCS)

After careful consideration, handling of lumbar injections will differ between the Month 24 CCS and CCS endpoints determined post Month 24, and in particular, for the primary Month 60 CCS to be used in Objective 1 analyses. As with the IDE study, lumbar injections that occur prior to two years post operatively are defined as Terminal Treatment Failures, Month 24 composite clinical failures and further follow-up is censored when summarizing effectiveness endpoints (i.e., ODI, VAS, ZCQ, treadmill). This is designed to (1) produce a composite endpoint that is sensitive to early device failure and to (2) avoid bias arising from inclusion of clinical data that could be reflecting successful secondary treatment of a failed index treatment. A different approach seems advisable for the Month 60 CCS endpoint for use in this 'real conditions of use' study. The goal is to avoid classifying calling transient symptom management as a device failure unless there is subsequent re-operation or unless patient status is compromised as reflected in lack of an ODI improvement from baseline that is less than 15%. Therefore, for Month 60 CCS, lumbar injections occurring within 12 months of the Month 60 visit will indicate Month 60 CCS failure (as well as those within the first 24 months post-surgery). This is because a lumbar injection within 12 months of the Month 60 visit can confound the Month 60 assessment. Similarly, when determining intermediate CCS at Month 36 and Month 48, lumbar injections within 12 months of these clinic visits will indicate CCS failure for that time point, but not necessarily for subsequent time points. However, patients with 2 or more series of injections will be defined at terminal failures, that is, as a CCS failure at that time point and all subsequent timepoints.

As noted above, handling of lumbar injections will differ between the Month 24 CCS and CCS endpoints determined post Month 24, and in particular, for the primary Month 60 CCS to be used in Objective 1 analyses. In sensitivity analysis, lumbar injections occurring at any time between surgery and Month 60 will be considered a treatment failure. All other endpoints in the Month 60 CCS analysis remain identical in the sensitivity analyses.

A lumbar injection is defined as any deep injection into the spine, typically under image-guidance, of steroids and/or other pharmacologic agents (e.g., facet injections or epidural injections by the

transforaminal, interlaminar, or caudal routes). Other types of injections are not treatment failures such as trigger point injections, intramuscular injection for systemic administration of steroids, dry-needling, prolotherapy, or acupuncture.

3.3. Secondary Endpoints

- ODI change compared to baseline at 24 and 60 months as a continuous variables and in terms of achieving at least a 15 point improvement[7].
- Change in Visual Analog Scale (VAS) for low back pain (on the 100 mm scale) after 24 and 60 months compared to baseline as a continuous variables and in terms of achieving a 20 point improvement.
- Change in right and left leg pain using a Visual Analog Scale (VAS) 100 mm scale after 24 and 60 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement. A separate analysis will be performed to compare VAS scores for the "worst" legs.
- Change of Zurich Claudication Questionnaire (ZCQ) after 24 and 60 months compared to baseline:
  - Symptom severity (range 1-5)
  - Physical function (range 1-4)
  - Patient satisfaction (range 1-4, no baseline)[8].
  - ZCQ Overall Success (≥2 of 3 of the following)
    - Improvement in symptom severity ≥0.5
    - Improvement in physical function ≥0.5
    - Satisfied or somewhat satisfied as defined by a score of ≤ 2.5 points on the patient satisfaction domain.
  - ZCQ Overall Success components
- Maintenance or improvement in EQ-5D compared to baseline
- Change from baseline to Month 24 and Month 60 in maximum walking time from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes.
- Change from baseline to Month 24 and Month 60 in time to symptoms from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes.
- Neurological status (no new or worsening, persistent neurological deficit)
- Radiography Endpoints
  - Assessment of significant migration of the implant or the complete expulsion (significant is defined > 5 mm).
  - Assessment of spinous process fracture.
  - Assessment of maintenance of foraminal height
  - Assessment of adjacent level disease determined by independent radiographic review
- Correlation of foraminal height changes to improvement of walking distance on a treadmill (after 24 and 60 months compared to baseline).

7 Pratt RK et al., The Reliability of the Shuttle Walking Test, the Swiss Spinal Stenosis Questionnaire, the Oxford Spinal Stenosis Score and the Oswestry Disability Index in the Assessment of Patients with Lumbar Spinal Stenosis. Spine Vol. 27 (1) pp. 84-91.

8 Stucki G et al., Measurement Properties of a Self-Administered Outcome Measure in Lumbar Spinal Stenosis. Spine. Vol. 21(7). pp. 796-803.

- The CCS will be modified to examine the effect narcotics use (opioids and/or opiates) has on treatment success rates. When comparing coflex® in conjunction with decompression to decompression alone, this modified Month 24 CCS will include:
  - No “Treatment Failure” on or before the exact 2-year anniversary of the index surgery. Treatment Failure will include:
    - No surgical intervention at the index level
    - No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level
  - No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 12 that do not resolve by Month 24.
  - No major device-related adverse event defined as an event simultaneously both ‘Serious’ and 'Definitely' according to independent Clinical Events Committee (CEC) related to the implant on or before the exact surgical two-year anniversary or exact five-year anniversary. In the decompression alone group, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery.
- No use of a narcotic (opioids or opiates) at Month 24.

4. Subjects and Methods

4.1. Study Design

This is a prospective, non-randomized study with concurrently enrolled controls involving up to 20 centers in the US to assess the safety and effectiveness of the coflex® Interlaminar Technology for the treatment of at least moderate leg/buttocks/groin pain with or without low back pain in patients with moderate to severe spinal stenosis. Covariate balance will be achieved through a rigorous application of propensity score subclassification.

4.2. Number of Subjects

The numbers of patients to be enrolled is 150 patients per group (300 total). This total will be increased by 15% to account for loss-to-follow-up. The sample sizes were increased by an additional 20% in control group and 5% in the study device group to account for trimming of control patients and possible trimming of study device patients during the propensity score design. Therefore, the total enrolled will be 186 coflex patients and 220 decompression control patients for a total enrollment of 406.

Patients will be enrolled into one of the treatment groups (Group A, without additional implant, Group B, with coflex® Interlaminar Technology.

Recruitment of about 5 patients per month is expected. Each site will be required to enroll at least 5 patients.

4.3. Inclusion Criteria

1. Radiographic confirmation of at least moderate lumbar stenosis, which narrows the central spinal canal at one or two contiguous levels from L1-L5 that require surgical decompression. Moderate stenosis is defined as > 25% reduction of the antero-posterior dimension compared to the next adjacent normal level, with nerve root crowding compared to the normal level, as determined by the investigator on CT Scan or MRI.* The patient may have, but is not required to have for inclusion in the study:
    a. Facet hypertrophy and subarticular recess stenosis at the affected level(s);
    b. Foraminal stenosis at the affected level(s);
    c. Up to stable Grade I degenerative spondylolisthesis (Meyerding classification) or equivalent retrolisthesis as determined by flexion/extension X ray:
        i. For single level disease, there may be up to a stable Grade I spondylolisthesis or equivalent retrolisthesis at the affected level as determined on flexion/extension films by the investigator.
        ii. For two level disease, there may be up to a stable Grade I spondylolisthesis or equivalent retrolisthesis at only one of the two contiguous affected levels as determined on flexion/extension films by the investigator. Patients with up to stable Grade I spondylolisthesis at two contiguous levels are excluded, but patients with up to Grade I stable spondylolisthesis at one level and equivalent retrolisthesis at the adjacent level may be included.
    d. Mild lumbar scoliosis (Cobb angle up to 25º)
2. Radiographic confirmation of no angular or translatory instability of the spine (instability as defined by White & Panjabi: Sagittal plane translation >4.5mm or 15% or sagittal plane

rotation >15° at L1-L2, L2-L3, and L3-L4; >20° at L4-L5 based on standing flexion/extension X-rays)

3. VAS back pain score of at least 50 mm on a 100 mm scale.
4. Neurogenic claudication as defined by leg/buttocks or groin pain that can be relieved by flexion such as sitting in a chair.
5. Patient has undergone at least one epidural injection at any prior time point, AND at least 6 months of prior conservative care without adequate and sustained symptom relief.
6. Skeletally mature
7. Oswestry Low Back Pain Disability Questionnaire score of at least 20/50 (40%).
8. Appropriate candidate for treatment using posterior surgical approach.
9. Psychosocially, mentally, and physically able to fully comply with this protocol, including adhering to scheduled visits, treatment plan, completing forms, and other study procedures.
10. Personally signed and dated informed consent document prior to any study-related procedures indicating that the patient has been informed of all pertinent aspects of the trial.

*The Lumbar Spine (H. Herkowitz ed. 2004, Lippincott Williams, & Wilkins).

4.4. Exclusion Criteria

1. More than two contiguous vertebral levels requiring surgical decompression.
2. Prior surgical procedure that resulted in translatory instability of the lumbar spine [as defined by White & Panjabi (see Inclusion Criteria, Item #2)].
3. More than one surgical procedure at any combination of lumbar levels.
4. Prior fusion, implantation of a total disc replacement, complete laminectomy, or implantation of an interspinous process device at index lumbar level.
5. Radiographically compromised vertebral bodies at any lumbar level(s) caused by current or past trauma or tumor (e.g., compression fracture).
6. Severe facet hypertrophy that requires extensive bone removal which would cause instability.
7. Isthmic spondylolisthesis or spondylolysis (pars fracture).
8. Degenerative lumbar scoliosis (Cobb angle of greater than 25°).
9. Disc herniation at any lumbar level requiring surgical intervention.
10. Osteopenia: A screening questionnaire for osteopenia, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients who require a DEXA bone mineral density measurement. If DEXA is required*, exclusion will be defined as a DEXA bone density measured T score of ≤ -1.0 (The World Health Organization definition of osteopenia).
11. Back or leg pain of unknown etiology.
12. Axial back pain only, with no leg, buttock, or groin pain.
13. Morbid obesity defined as a body mass index > 40.
14. Pregnant or interested in becoming pregnant in the next three years.
15. Known allergy to titanium, titanium alloys, or MR contrast agents.
16. Active or chronic infection – systemic or local.

17. Chronically taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids), not including a medrol dose pack.
18. History of significant peripheral neuropathy.
19. Significant peripheral vascular disease (e.g., with diminished dorsalis pedis or posterior tibial pulses).
20. Unremitting back pain in *any* position.
21. Uncontrolled diabetes.
22. Known history of Paget's disease, osteomalacia, or any other metabolic bone disease (excluding osteopenia, which is addressed above).
23. Cauda equina syndrome, defined as neural compression causing neurogenic bowel (rectal incontinence) or bladder (bladder retention or incontinence) dysfunction.
24. Fixed and complete motor, sensory, or reflex deficit.
25. Rheumatoid arthritis or other autoimmune diseases.
26. Known or documented history of communicable disease, including AIDS, HIV, active Hepatitis
27. Active malignancy: a patient with a history of any invasive malignancy (except nonmelanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least five years. Patients with a primary bony tumor are excluded as well.
28. Prisoner or ward of the state.
29. Subject has a history of substance abuse (e.g., recreational drugs, narcotics, or alcohol).
30. Subject is currently involved in a study of another investigational product for similar purpose.
31. Currently seeking or receiving workman's compensation.
32. In active spinal litigation.

*Primary location for DEXA scan should be the spine. In the event that the spine T score is in the osteopenic range (-1.0 to -2.5) then a T-Score from the hip may be obtained. If the T-Score from the hip comes back above -1.0 then, at the discretion of the investigator, the patient may be considered for inclusion in the study. Also, a hip DEXA may be used in the event that a spine DEXA cannot be obtained.

4.5. Restriction to Subjects

There are no study specific restrictions for patients' diet or habits (smoking, etc.…).

4.6. Study Conduct

The study will be performed in up to 20 study centers in the US (10 coflex sites and 10 control sites). All centers are experienced in the treatment of spinal stenosis with decompression surgery and with the coflex® Interlaminar Technology, but no site were included in the IDE study. Each site will enroll either coflex patients or control patients. Sites will be selected for comparability in terms of surgeon and institutional characteristics as well as for expected patient mix characteristics. All treatments will be carried out according to the routine procedures for decompression surgery in each center. Only investigators that are experienced in the implantation of the study device will perform the surgeries for this trial.

Subjects participating in this study will be recruited from the investigators' standard patient populations. Subjects must meet all of the following inclusion criteria and none of the exclusion criteria. The investigator maintains exclusive responsibility for the inclusion and exclusion of any potential study participant.

All patients presenting for treatment of symptomatic spinal stenosis that have not responded to conventional medical therapy will be evaluated for study participation based on the inclusion/exclusion criteria. Subjects will be considered enrolled in the study after informed consent has been signed and at time of surgical incision.

The target enrollment is 406 patients (186 coflex patients and 220 decompression control patients). A minimum of 345 patients are planned to be included in the trial. Each center should recruit at least 5 patients.

The schedule of study related actions is summarized in the Study Timeline (see Section 4.8.9).

Patients who fulfil the in-/exclusion criteria will be enrolled into one of the two concurrent treatment groups.

Group A: decompression surgery without any further stabilization (control group)

Group B: decompression surgery with stabilization using the coflex® Interlaminar Technology (treatment group)

Blood sampling is not planned as a part of the trial but might be performed as part of the routine procedures of each center. Blood parameters will not be documented in the CRF – except if necessary for SAEs.

For the implantation of the coflex® Interlaminar Technology the product brochure and implantation instructions provided by the manufacturer have to be followed.

4.7. Description of Study Procedures

4.7.1. Surgical Technique

Selective, microsurgical decompression surgery will be performed through a mono- or biportal access based on the experience of the investigators, taking into consideration the individual situation of each patient.

Wing bending pliers provided by Paradigm Spine will be used for controlled bending and crimping of the coflex® implant wings if necessary.

4.7.2. X-ray Imaging:

X-ray images will be made **in standing position** in both cohorts.

During visit 1, visit 3, visit 4, visit 5, visit 6, visit 7, and visit 8 X-rays will be taken in the following positions: antero-posterior, lateral, flexion and extension.

During visit 2 (surgery) X-rays will be taken only in group B (with coflex® implant) for the following two positions: antero-posterior and lateral.

In total 30 X-ray images will be made in the course of the trial for group B (with coflex® implant).

In total 28 X-ray images will be made in the course of the trial for group A (without implant; control).

X-ray images from Visit 2, which are only performed in test group B, will not be evaluated on regular basis, but may be consulted on demand for potential assessment of spinous process fractures, implant function and potential migration.

Additional radiographs may be taken in between regularly scheduled visits at the discretion of the investigator/patient's surgeon due to new symptoms. This additional information makes an earlier intervention possible, which could result in an early reduction of the pain and/or in a delay in progression of the illness.

4.7.3. Questionnaires

- The **Oswestry Low Back Pain Disability Index (ODI**) will be used. The ODI is a self-rating patient questionnaire developed to assess the impairment on patients' life by low back pain. The ODI is used as part of the primary effectiveness endpoint of this trial.

- The **Zurich Claudication Questionnaire (ZCQ)** will be used as a self-rating patient questionnaire to assess the impact of pain on patient's everyday life. The ZCQ includes questions that are used to produce indices of symptom severity, physical functional status and patient satisfaction.

- **Visual Analog Scales (VAS)** will be used. They comprise of a 100 mm horizontal line which is scaled from 0 (left end) to 10 (right end). Every VAS is associated with a single question. The patient will be asked to mark his subjective impression about the question asked by a small vertical line on the VAS. For evaluation the distance of this marking from the left end of the VAS will be measured in mm with a ruler. VAS questions include right leg pain, left leg pain, and back pain.

- The **EQ-5D** will be used. The EQ-5D consists of 5 questions and a drawn scale to measure the patient's quality of life.

It is important, that VAS scores, ODI, ZCQ, and EQ-5D are filled in by the patient prior to walking distance test.

- **Patient Satisfaction Questionnaire**
  Patients will be asked in a questionnaire for their subjective satisfaction with the result of the treatment (4 grading levels) and if they would again agree to a surgical treatment if they would have to make the decision again (yes / no).

- **Questionnaire about employment**
  Patients will be asked about their employment status, workman's comp status and treatment satisfaction.

<u>Information of Patients on Questionnaires</u>

All questionnaires and VAS will be explained to the patient extensively by the investigator. The patients will not have access to the questionnaires / VAS which they have filled in during prior visits. The questionnaires / VAS should be filled in by the patients themselves; they should not be influenced by the investigator or other persons.

4.7.4. Direct Data Capture

All documents that are used on site are considered source. All patient questionnaires are defined as direct data capture pages and they represent the source of the captured data (for monitoring they will be monitored as source data and there will be no other source for these data). The study coordinator will enter the source data onto the eCRF's. The monitors will verify the source documents match the eCRF's. Once this has been verified the data manager will lock the field so the data cannot be changed unless requested from the data manager.

The data will be entered into a validated electronic database capture (EDC) system: OpenClinica. The data manager will be responsible for programming of the database and data management. The Investigator or his/her designee is responsible for data entry at the time of the subject visit. The site CRA and data manager will review the data for completeness and accuracy compared to source documents (e.g., medical charts, hospital records, etc.). The CRA, data manager, or Sponsor can initiate queries where data is inconsistent or incorrect. Queries are entered, tracked, and resolved through the EDC system directly.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

4.7.5. Neurological Status

Neurological status will be evaluated by:

- Muscle strength (listed for nerve roots from L3, L4, L5, S1; scoring from 0 to 5)
- Sensory deficits (listed for nerve roots from L3, L4, L5, S1; defining status)
- Reflex
- Straight Leg Raise

4.7.6. Walking Distance Test

During this test a patient has to walk on a treadmill (speed 1.2 miles/hour[9,10]) for 15 min. If the patient cannot keep up for the complete 15 min the maximum time that he was able to walk on the treadmill will be captured. The corresponding walking distance will be calculated.

The person conducting the walking test (i.e., physician, therapist, PA) must check whether a patient shows any medical symptom that contradicts an exercise test on the treadmill (e.g. heart problems). If the patient is not able to perform the walking distance test at any of the clinical visits it does not lead to exclusion for the study.

4.7.7. Central Evaluation of Radiological Images

Only sites with digital X-ray capability will enroll patients into this study.

---

9 Deen H. et al., Measurement of exercise tolerance on the treadmill in patients with symptomatic lumbar spinal stenosis: a useful indicator of functional status and surgical outcome, J. Neurosurg 83:27-30, 1995

10 Deen H. et al., Use of the Exercise Treadmill to Measure Baseline Functional Status and Surgical Outcome in Patients With Severe Lumbar Spinal Stenosis, Spine: Volume 23(2) 15 pp 244-248, 1998

In order to achieve a comparable evaluation, all radiological images will be evaluated by a core lab. For evaluation of X-rays a special form “core evaluation of X-rays” is available. All relevant parameters are listed in this special case report form.

X-ray images will be sent electronically to the core lab, either on a CD or via mail or via FTP site.

Anonymized electronic copies will be stored at sponsor and might be used for external reading and evaluation in the future.

Preoperative MRI images, 24 Month CT images, and 60 Month CT images for subjects with symptomatic, confirmed spinous process fracture will also be collected. Fractures are confirmed by the core lab.

4.7.8. Assessment of Concomitant Medication:

Pain Management

The investigator will ask the patient for detailed information on all pain killers taken. The type of pain killers used by the patient (Visit 1 – Visit 5) will be captured via the eCRF. It will be differentiated between the following types of pain killers: Class II narcotics, other narcotics (“Tramadol”, “Tilidin”), NSAIDs including acetylsalicylic acid (“Aspirin”) and acetaminophen (“Paracetamol”). It will be analyzed if pain killers were not used any more or if less strong pain killer classes are used. Other kind of pain management such as epidural steroid injection, facet injection or nerve root block will be documented in the eCRF (Visit 1, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8).

Other Concomitant Medication

Concomitant medication will not be recorded except if they are related to an SAE or might have impact on the study evaluation according to the investigators decision.

4.7.9. Physical Examination

A detailed physical examination will be performed at Visit 1. In the following visits only a routine physical examination will be performed and changes compared to screening will be recorded. The investigator is free to perform a complete physical examination.

Medical history will be documented in the medical history form only. Medical history will be source verified through source document worksheets and medical records.

4.7.10. Follow Up Treatment after Discharge

There are no study related limitations to the routine follow up treatment (e.g., use of orthoses, physiotherapy). The follow up treatment will be recorded in the eCRF until Visit 8.

4.7.11. Informed Consent

Before any trial related action will be performed, a **written informed consent** will be obtained from each patient or the legal representative after adequate patient information; this includes the handing over of the written patient information and informed consent form that was approved by the IRB. During this procedure the investigator informs the patient extensively about all aspects of the trial. The patient will have an opportunity to ask questions.

4.8. Description of Study Visits

4.8.1. Visit 1: Screening (< 4 weeks before day 0)

This visit can be performed up to 4 weeks before day 0 (day of surgery) or even at the same day of surgery as long as the patient gets sufficient time to think over the study participation after being informed by the investigator.

- During the screening visit the **ODI, ZCQ, EQ-5D and VAS back pain** and **VAS leg pain** of the patient will be assessed as baseline level (baseline for ZCQ patient satisfaction is assessed at the first post-operative visit at visit 3 as these questions only concern post-operative aspects). A questionnaire about **status of employment / pension** will be filled in by the patient.
- Demographic and medical history data (including weight, height, race, etc.), data about pain **management** as well as a **physical examination** will be assessed as routinely done at each center.
- It will be documented in the eCRF which prior therapy had been performed for back- and leg-pain (epidural injection, facet injection, nerve root block).
- The **Body Mass Index** (BMI) will be determined by the investigator as this is one of the exclusion criteria. BMI = body weight: (body height in m)^2. The unit of the BMI is kg/m^2.
- Only if all **in-/exclusion criteria** are fulfilled (as far as assessable before surgery) the patient will be considered for surgery. In case any in/exclusion criterion is not fulfilled prior to enrollment this patient will be judged as a screening failure and will not receive a patient number.
- For screening failures only the informed consent, patient identification data and the reason for failure will be monitored by the study monitor. Screen failures will be replaced by new patients in order to achieve 406 treated study patients.
- As baseline levels a **Walking Distance Test** will be performed and the **Neurological Status** will be assessed.
- **X-ray images** necessary for inclusion must be available in anterior-posterior position as well as in lateral position and in flexion and extension and should not be older than 6 months.
  Images will be taken to evaluate in-/exclusion criteria (e.g. exclusion of isthmic spondylolisthesis or spondylolysis). Translatory instability has to be excluded utilizing functional X-rays (≤ 3 mm).
  All X-ray images are made in standing position.
- Necessary routine **MRI** (Post-Myelo-CT is also permitted in the event that the patient already has one that is <6 months old) images must be available and should not be older than 6 months. They are obligatory for a clear definition of the medical indication (spinal stenosis) of the study patient. Further MRI imaging is not planned for this trial. The cross-sectional area of the spinal canal an foraminal area at the levels to be decompressed will be collected at baseline.

4.8.2. Visit 2: Surgery

- Completion of in/exclusion criteria
- Surgery
- Hospitalization information will be collected such as duration of surgery, blood loss and number of days in hospital.

- Discharge Information: Date of discharge, neurological status, pain management, follow-up treatment. X-rays have to be performed before discharge only in group B (with implant) in anterior-posterior and lateral position.
- Exclusion during the decompression surgery:
  In case the surgeon identifies during surgery any circumstance that contradicts to the patient's participation in the trial, the surgeon has to exclude the patient from the trial participation. Possible exclusion reasons are:
  - Instabilities assessed during surgery that requires stabilization by spinal fusion.
  - Partial resection or resection of disc tissue (see exclusion criterion 2).
  - (S)AEs assessed during surgery that rule out the implantation of coflex® (e.g. breakage of a spinal process, local osteoporosis).
- As these patients had been enrolled an eCRF will be filled in. The study monitor will only check the signed informed consent form and patient demographics as well as the reason of failure. The patient will be a dropout and the dropout reason will be recorded in the eCRF.

4.8.3. Visit 3: 3 months follow up (±2 weeks)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- Walking distance test

4.8.4. Visit 4: 12 months follow up (±2 month)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- Walking distance test

4.8.5. Visit 5: 24 months follow up (±2 month)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization

- Follow up treatment
- X-ray images for both groups in all four positions
- CT Scan for all subjects
- Walking distance test

4.8.6. Visit 6: 36 months follow up (±4 month)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- Walking distance test

4.8.7. Visit 7: 48 months follow up (±4 month)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- Walking distance test

4.8.8. Visit 8: 60 months follow up (±4 month)

- VAS leg pain
- VAS back pain
- Questionnaires ODI, ZCQ, EQ-5D, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- CT Scan for symptomatic, confirmed spinous process fracture subjects
- Walking distance test

4.8.9. Common Events

- Unscheduled Events – Visits that occur outside of the scheduled set of visits
    - VAS leg pain
    - VAS back pain
    - Questionnaires ODI, ZCQ, EQ-5D, and patient satisfaction
    - Walking-Distance Test

- Secondary Surgical Interventions (SSI)
  - VAS leg pain
  - VAS back pain
  - Questionnaires ODI, ZCQ, EQ-5D, and patient satisfaction
  - Walking Distance Test
  - SSI detail form
- Adverse Events (events occuting after the time of incision).

4.8.10. Schedule of Study Visits

A tabular summary of visit schedule is provided below.

	Screening	Follow-Up							
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
	< 4 weeks before d0	**day 0 surgery**	**3 months after surgery (±2 weeks)**	**12 months after surgery (±2 month)**	**24 months after surgery (±2 month)**	**36 months after surgery (±4 months)**	**48 months after surgery (±4 months)**	**60 months after surgery (±4 months)**	**Final Report**
Patient information and Informed consent	X								
Demographics	X								
Medical history	X								
Pain management	X	X[3)]	X	X	X	X	X	X	
Physical examination	X[1)]		X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	
Neurological status	X	X[3)]	X	X	X	X	X	X	
Inclusion/exclusion criteria	X	(X)							
X-ray in standing position (AP, lateral, flexion, extension)	X	X[2) 3)]	X	X	X[4)]	X	X	X[4)]	
MRI and/or Post Myelo CT (not older than 6 months)	X								
Diagnosis	X								
Walking Distance Test (treadmill)	X		X	X	X	X	X	X	
VAS back pain, VAS leg pain	X		X	X	X			X	
ODI, ZCQ, EQ-5D	X		X	X	X	X	X	X	
Surgery		X							
Patient's satisfaction questionnaire			X	X	X	X	X	X	
Documentation of AEs		X	X	X	X	X	X	X	

1) A detailed physical examination will be performed at visit 1. In the following visits only a routine physical examination will be performed and changes compared to screening will be recorded. The investigator is free to perform a complete physical examination.
2) Only group B (with coflex® implant: anterior-posterior, lateral).
3) After surgery, before discharge.
4) CT Scans will be conducted at 24 months for all subjects and at 60 months for all symptomatic, confirmed spinous process fracture subjects.

4.9. Device Accountability:

The coflex® devices are marked with a lot number. An individual serial number is not available. For the trial routinely delivered coflex® devices that are available at each center are used. There will not be any trial specific device shipments and therefore device accountability will not be performed.

Charge number and size of the coflex® implants used with every study patient will be documented in the eCRF.

4.10. Travel Cost Compensation:

Every patient will receive travel cost compensation up to $100 pending IRB approval. The travel expenses will be provided to the patient by the investigator/coordinator.

4.11. Sample Storage and Shipment:

There are no study related collections of blood samples or any other body fluids. If required, blood samples etc. will be collected and processed according to the routine procedures of the centers.

4.12. Analysis Sets:

The following analysis sets are defined.

Intent-To-Treat Analysis Set – Propensity Score Selected (ITT–PS Selected): The ITT–PS Selected analysis set will include all subjects enrolled into the study or control groups in which treatment was attempted as defined by the recording of incision time. Subjects will be classified by the group in which they are enrolled, regardless of whether or not that treatment was actually completed. Intraoperative failures will be included in primary hypothesis testing as composite clinical endpoint failures. Primary efficacy analyses will be conducted using the ITT – PS Selected analysis set. A subject must be selected into a PS subclass in order to be included in this analysis set. The PS subclassification procedure is designed to retain all subjects receiving the study device, if possible. Since selection into a PS subclass is the observational study equivalent to randomization in a randomized study, control subjects not selected into a PS subclass will not be included in the ITT – PS Selected analysis set and not included in primary effectiveness and safety analyses. Non-selected subjects are referred to as ‚trimmed'. Safety data will be summarized separately for trimmed controls.

Completers Analysis Sets: Completers analysis sets will be defined at ITT–PS Selected evaluable for composite clinical success.

Safety Analysis Set: The Safety analysis set will include all subjects in the ITT–PS Selected analysis set plus study device patients who were not selected into a PS subclass, if any. Study device patients who were not selected into a PS subclass will be assigned to the subclass with the largest propensity scores for analyses that control for PS subclass. Primary safety analyses will be conducted using the Safety analysis set.

Per Protocol Analysis Set (PP): The PP analysis set will include subjects in the ITT–PS Selected analysis set with no major protocol violations of inclusion or exclusion criteria, as determined by

the Clinical Events Committee (CEC) and who are evaluable for the Month 24 composite clinical success endpoint (Objective 2, 3, and 4) or evaluable for the Month 60 CCS (Objective 1). It may also exclude subjects with confounding medical events or treatments following index surgery that are expected bias determination of the primary composite clinical success endpoint, as determined by the CEC. Secondary efficacy analyses will be conducted using the PP analysis set.

4.13. Subject Discontinuation

Patients which did not receive a patient number will be replaced – they will be judged as screening failures. At the end of the initial recruitment phase of 406 patients that fulfil all in-/exclusion criteria should be allocated to the study.

In order to meet 406 treated study patients those patients that are excluded by the investigator during the surgery will be replaced.

The patient is entitled to terminate the clinical investigation at any time without giving any reason and without having to expect any disadvantages by the Investigator.

Reasons for withdrawal of a patient from the clinical investigation may be:

- Insufficient cooperation of the patient (non-compliance with study procedures);
- Technical or administrative reasons (change of Investigator, move of the patient);
- Withdrawal of Informed Consent.
- Death

Pregnancy will not be a reason for discontinuation. The number of x-rays taken will be limited.

For patients who terminate the clinical investigation prematurely, a complete final examination has to be performed if the patient is still available for an examination.

For this final examination all assessments as planned for Visit 5 have to be carried out.

If the patient cannot come to a final examination the Investigator should clarify the reason and time point for discontinuation/drop out by phone and document this in the source document used at the site. In case of drop outs due to an (S)AE the Adverse Event has to be documented sufficiently in the SAE form and the Investigator has to report the SAE to the sponsor within 24 hours (see section about SAE reporting).

4.14. Trial Materials

4.14.1. Description of the Study Device

As the coflex implant is approved for market, the devices used for the study originate from the normal production and have to be handled according to the product brochure and manufacturers information.

4.14.2. Labeling

As the study device (coflex Implant) is already PMA approved, the devices used for this trial will not be labelled separately for this trial, i.e. no text like “for clinical investigation only” will be mentioned. Devices from the normal production will be used and the legal requirements for labelling PMA-approved (US) will be fulfilled.

4.14.3. Device Accountability

There will be no device shipments because of the trial. The devices routinely available at each center will be used for the study patients.

A device accountability form will therefore not be filled in. Any coflex device used with a patient will be documented (lot no. and size) in the eCRF.

4.15. Trial Documents:

The following documents have to be available before shipment of trial supplies to the trial center:

- A signed protocol and amendment(s), if any;
- A copy of the dated and signed written approval from the IRB of the protocol, amendment(s) (if any), Informed Consent Form, and any applicable recruiting materials. This approval must clearly identify the trial by title and number;
- A statement if the IRB is compliant with ICH-GCP guidelines, the names of the current members or composition of the IRB and their position in the health-care institution or their credentials, and the working procedures of the committee.
- Regulatory authority approval
- Signed Investigator's agreement (modified FDA Form 1572), if applicable,
- FDA Financial Disclosure Questionnaire, if applicable,
- A copy of the Signature Authorization Log that enlists all people involved in the trial at a center;
- The curricula vitae of the Investigator, co-Investigators and other study material (if any);
- The signed Financial Agreement.

4.15.1. Electronic Case Report Forms (eCRFs)

Electronic Case Report Forms (eCRFs) are to be completed for all subjects.

All data is entered into the Electronic Clinical Data Management System by the Study Coordinator or by the patient directly (patient questionnaires).

The Investigator must verify that all data entries in the eCRFs are accurate and correct. If certain information is "Not Done", "Not Available" or "Not Applicable", the Investigator must enter "n.d." or "n.av." or "n/a", respectively, in the appropriate space.

All data will be reviewed for consistency and correctness with the protocol by the Data Management team at the CRO. All discrepancies requiring verification via an examination of the source documents will be sent to the study site for resolution or resolved during Monitoring visits. During monitoring visits, the Clinical Research Associate (CRA) will also review all data, evaluate for completeness and have the study coordinator enter missing information and/or resolve errors with the Investigator. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee.

An electronic audit trail will be maintained to track all changes to the database.

4.15.2. Documentation Files

The Sponsor's Investigator file will include all relevant documents that are filed in the Investigator file and additional internal information (e.g., internal communication Sponsor-CRO). The CRO file will contain all study related documents including all internal and external communication.

All data about X-rays will be kept for at least 30 years after completion of the study.

4.15.3. Essential Documents for the Conduct of a Clinical Trial

The Investigator file will be provided to the Investigator at the Study Initiation Visit. It is required by law that the Investigator keeps this file updated and in good condition during the entire study.

The Investigator file contains the essential documents for the conduct of a clinical trial:

- Instructions for Use
- Protocol and Amendment(s)
- Protocol and Amendment(s) Signature Page(s)
- Financial Disclosure(s) for Investigator and Sub-Investigator(s)
- Core Laboratories Certifications and Procedures
- Investigator Agreement or FDA Form 1572
- Delegation of Authority Log
- Curriculum Vitae (Investigator, Sub-Investigator(s), Study Staff)
- Medical License (Investigator, Sub-Investigator(s), Study Staff)
- Subject Protection/GCP Training (Investigator, Sub-Investigator(s), Study Staff)
- IRB Submissions/Approvals:
    - Original Study/Protocol
    - Protocol Amendments
    - Informed Consent (all version)
    - Advertisements
    - Other Written Subject Information
- Interim or Annual Reports to IRB/EC
- Site Specific SAE/UADE Reports to IRB/EC
- Site Specific Deviation Reports to IRB/EC
- IRB Membership List, Assurance Number or Statement of Compliance
- Subject Screening and Enrollment Log
- Monitoring Visit Sign-In Log
- Clinical Trial Agreement
- Monitoring Visit Confirmation and Follow-Up Communications
- Study Communications

4.16. Archiving:

The Investigator shall maintain the Investigator file, which contains the trial documents as specified in “Essential Documents for the Conduct of a Clinical Trial” mentioned above and as required by the applicable regulatory requirement(s).

The Investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents shall be retained for 2 years in the study site and with the Sponsor after completion of the study. Under no circumstances shall the Investigator relocate or dispose any trial documents before having obtained written approval of Paradigm Spine. This also applies if the archiving period of 2 years has come to an end.

Any difficulty in storing original documents must be discussed with the Clinical Research Associate as soon as possible.

5. Performance Evaluation and Measurements

5.1. Primary Variables of Performance

Month 60 composite success will require the following items (Objective 1):

- At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100).
- No reoperations, revisions, removals, or supplemental fixation at the index level(s);
- No ≥2 injections or series of injections for any lumbar level**, or nerve block procedures performed to treat spinal stenosis at any lumbar level(s); or a single injection within 12 months of the 5 year endpoint.

  **A series of injections is considered 2-3 injections performed between 24-hour and one week intervals designed to treat a single pain event. Secondary injections performed due to patient demand or recurrence of symptoms following the initial injection are considered separate injections and would constitute a study failure.

For Objectives 2 and 3, the Month 24 CCS from the IDE will be slightly modified to include any surgical intervention at index level(s). This is because the decompression only group receives no device. In summary, when comparing coflex® in conjunction with decompression to decompression alone, Month 24 CCS will require.

- No “Treatment Failure” on or before the exact 2-year anniversary of the index surgery).
- At least a 15 point improvement relative to pretreatment baseline in the Oswestry Disability Index (ODI, range 0-100).
- No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 12 that do not resolve by Month 24.
- No major device-related adverse event defined as an event simultaneously both ‘Serious’ and 'Definitely' related to the implant on or before the exact surgical two-year anniversary.

Treatment Failure will include:

- No surgical intervention at the index level
- No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level.

The identical Month 24 CCS endpoint used in the IDE study will be used to compare PAS results to IDE study results and to update the Bayesian posterior probabilities of non-inferiority and superiority relative to fusion (Objective 4).

5.1.1. ODI

Improvement in the Oswestry Disability Index (ODI) is the primary clinical status indicator among non-Treatment Failures. ODI has become one of the principal condition-specific outcome measures used in the management of spinal disorders.[11] The ODI is a self-rating patient questionnaire that is comprised of ten items that reflect patients’ ability to manage their everyday life while dealing with their pain. Every selectable answer is linked to an amount of points from 0 to 5. A maximum of 50 points can be reached. The primary variable will be expressed as a percentage of the maximum possible value. The following are interpretations of these percentages: 0% to 20% - minimal disability; 21% to 40%, moderate disability; 41%-60% severe

11 Fairbank J.C.T., The Oswestry Disability Index, Spine Volume 25, Number 22, pp 2940–2953, 2000

disability; 61%-80% - crippled; 80% to 100%, bed-bound or exaggerating symptoms. An increase from baseline of 15 is required for primary composite clinical success.

5.1.2. Secondary Surgical Interventions

Reoperations, revisions, removals and supplemental fixation are defined as follows:

- A revision is a procedure that adjusts or in any way modifies or removes part of the original implant configuration, with or without replacement of a component. A revision may also include adjusting the position of the original configuration.
- A removal is a procedure where all of the original system configurations are removed with or without replacement.
- A reoperation is any surgical procedure at the involved level(s) that does not remove, modify, or add any components to the system. Note: a surgery to alleviate post-operative superficial wound problems within the immediate post-operative 30 day window will not be considered a treatment failure.
- A supplemental fixation is a spinal procedure in which additional instrumentation not under study in the protocol is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system) at the index level(s).

If a subject in either study group undergoes a reoperation, revision, removal, or supplemental fixation procedure, the subject should remain in the study and should continue to be followed up within the study. Such patients will be considered a Treatment Failure.

5.1.3. Lumbar Injections

All lumbar injections will be captured as part of the study. A lumbar injection is defined as any deep injection into the spine, typically under image-guidance, of steroids and/or other pharmacologic agents (e.g. facet injections or epidural injections by the transforaminal, interlaminar, or caudal routes). Other types of injections such as trigger point injections, intramuscular injection for systemic administration of steroids, dry-needling, prolotherapy, or acupuncture, will be captured but will not beconsidered study failures.

Any patient receiving a lumbar injection including epidural injection, nerve root blocks and facet blocks on or before the Month 24 is considered a Treatment Failure and so will not have achieved Month 24 composite clinical success. Patients receiving a lumbar injection within 12 months of their Month 60 interval will be failures for Month 60 CCS since their clinical data is no longer evaluable due to the potential confound of a successful secondary treatment for a failed index treatment. Similarly, when determining intermediate CCS at Month 36 and Month 48, lumbar epidural injections within 12 months of these clinic visits will indicate CCS failure for that time point, but not necessarily for subsequent time points. Additionally, patients receiving 2 or more series of injections as defined above will be CCS failures for all later time points. A separate sensitivity analysis will also be performed within Objective 4 where all patients who receive lumbar injections at any time prior to Month 60 will be counted as Treatment Failures.

5.2. Secondary Variables of Performance

Secondary evaluation criteria include:

- ODI change compared to baseline at 24 and 60 months as a continuous variables and in terms of achieving at least a 15 point improvement.
- Change in Visual Analog Scale (VAS) for low back pain (on the 100 mm scale) after 24 and 60 months compared to baseline as a continuous variables and in terms of achieving a 20 point improvement.

- Change in leg pain using a Visual Analog Scale (VAS) 100 mm scale after 24 and 60 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement.
- Change of Zurich Claudication Questionnaire (ZCQ) after 24 and 60 months compared to baseline:
  - Symptom severity (range 1-5)
  - Physical function (range 1-4)
  - Patient satisfaction (range 1-4, no baseline)[8]
  - ZCQ Overall Success (≥2 of 3 of the following)
    1. Improvement in symptom severity ≥0.5
    2. Improvement in physical function ≥0.5
    3. Satisfied or somewhat satisfied as defined by a score of ≤ 2.5 points on the patient satisfaction domain.
  - ZCQ Overall Success components.
- Maintenance or improvement in EQ-5D compared to baseline.
- Change from baseline to Month 24 and Month 60 in maximum walking time from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes.
- Change from baseline to Month 24 and Month 60 in time to symptoms from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes
- Neurological status (assessment of maintenance of improvement after surgery throughout study duration)
- Radiography Endpoints
  - Assessment of significant migration of the implant or the complete expulsion (significant is defined > 5 mm).
  - Assessment of spinous process fracture.
  - Assessment of maintenance of foraminal height
  - Assessment of adjacent level disease determined by independent radiographic review
- Correlation of foraminal height changes to improvement of walking distance on a treadmill (after 24 and 60 months compared to baseline). No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 12 that do not resolve by Month 24. For Month 60 CCS, this will be established by identifying new or worsening deficits at Month 48 that do not resolve by Month 60.
- Presence of a major device-related adverse event defined as an event simultaneously both ‘Serious’ and 'Definitely' related to the implant on or before the exact surgical two-year anniversary or exact five-year anniversary.
- The CCS will be modified to examine the effect narcotics use (opioids and/or opiates) has on treatment success rates. When comparing coflex in conjunction with decompression to decompression alone, this modified Month 24 CCS will include:
  - No “Treatment Failure” on or before the exact 2-year anniversary of the index surgery. Treatment Failure will include:
  - No surgical intervention at the index level
  - No lumbar epidural steroid injection including nerve root blocks and facet blocks at any lumbar level
  - No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 12 that do not resolve by Month 24.
  - No major device-related adverse event defined as an event simultaneously both ‘Serious’ and 'Definitely' according to independent Clinical Events Committee (CEC) related to the implant on or before the exact surgical two-year anniversary or exact

five-year anniversary. In the decompression alone group, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery.
- No use of a narcotic (opioids or opiates) at Month 24.

5.2.1. Walking Distance Test on a Treadmill

Patients will perform a walking distance test on a treadmill at screening (visit 1) and post-operatively. It will be assessed if a patient can walk on the 0° ramp incline at a speed of 1.2 miles/hour) for 15 minutes (according to the publication by Deen[9]).

Also assessed will be time to first symptoms, time to severe symptoms and nature of symptoms (leg weakness, leg pain, back pain, or generalized fatigue, other). A time of zero will be recorded when symptoms were present at onset. The examination will be stopped after 15 minutes or at the onset of severe symptoms.

Definition of severe symptoms is: The level of discomfort that would make patients stop their activities in usual life situations. Patients will be instructed to walk with an upright posture. They are not permitted to lean forward or to hold onto the handrails during examination.

It is assumed that patients with additional back pain will have more problems in managing the complete walking distance and therefore may stop the walking distance test before the endpoint at 15 min.

The investigator has to check whether the patient shows any medical contraindication against the performance of a walking distance test (Deen 1995, p 28).[9]

If the patient is not able to perform the walking distance test at any of the clinical visits it does not lead to an exclusion of the study.

In summary, the primary endpoints from the treadmill test will be:

- Change from baseline to Month 24 and Month 60 in maximum walking time from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes.
- Change from baseline to Month 24 and Month 60 in time to symptoms from treadmill test as a continuous variable and in terms of achieving at least an 8 minute improvement or maximum time of 15 minutes.

5.2.2. VAS

Change in Visual Analog Scale (VAS) for low back pain (on the 100 mm scale) after 24 and 60 months compared to baseline as a continuous variables and in terms of achieving a 20 point improvement.

Change in right leg pain and left leg pain using a Visual Analog Scale (VAS) 100 mm scale after 24 and 60 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement.

5.2.3. Zurich Claudication Questionnaire (ZCQ)

Change of Zurich Claudication Questionnaire (ZCQ) after 24 and 60 months compared to baseline:

- Symptom severity (range 1-5)
- Physical function (range 1-4)
- Patient satisfaction (range 1-4, no baseline)
- ZCQ Overall Success (≥2 of 3 of the following)
  - Improvement in symptom severity ≥0.5
  - Improvement in physical function ≥0.5
  - Satisfied or somewhat satisfied as defined by a score of ≤ 2.5 points on the patient satisfaction domain.
- ZCQ Overall Success components

5.2.4. EQ-5D

Maintenance or improvement in EQ-5D (quality of life) after 24 and 60 months compared to baseline.

5.2.5. Neurological Changes

No persistent new or worsening sensory or motor deficit where persistence is established by identifying new or worsening deficits at Month 18 that do not resolve by Month 24 for assessment of Month 24 CCS. Each individual assessment is evaluated separately by side (right or left) and by anatomic location as appropriate. Any specific sub test that indicates a deficit at Month 18 that was not present at baseline or for which there is a worsening at Month 18 relative to baseline that does not return to baseline or better status by Month 24 will be identified. Specific sub tests will be aggregated into summary endpoints (e.g., muscle strength deficit and sensory deficit) as well as into an overall summary variable that is included in the overall composite clinical success endpoint.

A similar definition will be will be used for Month 60 CCS. No persistent new or worsening sensory or motor deficit where persistence will be established by identifying new or worsening deficits at Month 48 that do not resolve by Month 60 for assessment of Month 60 CCS.

5.2.6. Migration

Assessment of significant migration of the implant or complete expulsion (significant is defined > 5 mm) will be assessed from X-ray images (point of reference is the tip of the U-portion implant identified on the corresponding X-ray image). Baseline images will be made before discharge of the patient. Further images will be made after 3 months and after 24 months, and annually thereafter. All X-ray images from all centers will be evaluated centrally by an experienced radiologist.

5.2.7. Spinous Process Fracture

Spinous process fractures will be assessed from X-ray at all time points and CT at 24 months. Subjects with confirmed, symptomatic spinous process fractures will also have CT taken at 60 months. All X-rays and CTs from all centers will be evaluated centrally by an experienced, independent radiologist. Presence of spinous process fractures will not be considered a treatment failure.

6. Study Criteria for Safety

The safety assessments will include documentation of Adverse Events and SAEs and device/procedure related adverse events (e.g. breaking of implants). Specific AEs will be summarized according to incidence (per patient) and counts of AE over time. Further, the following criteria will be documented:

- Assessment of revisions and additional stabilizations.
- Assessment of epidurals.
- Assessment of narcotics usage.

6.1. Adverse Events:

At each visit all adverse events, whether voluntarily reported by the patient or observed by the investigators, will be recorded in the appropriate eCRF. Data collected will include:

- Description of sign or symptom,
- Date of start and date of end of the adverse event,
- Event severity (mild, moderate, severe),
- Frequency (once/intermitting/continuous),
- Relation to treatment (definite, probable, possible, unlikely, not related),
- Event treatment (e.g., none, non-drug therapy, medications, injection)

An AE is any undesirable clinical occurrence in a subject whether or not it is related to the device/procedure. Any condition at baseline that is recorded as a preexisting condition is not an AE unless it worsens in intensity or duration. The collection of AEs will begin in the operating room when the incision(s) is made that starts the treatment procedure. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device/procedure related, will be reported in detail on the appropriate eCRF and followed to resolution.

The description of the AE will include the date and time of onset, severity, causal relationship to the device or procedure, any treatment required, and the outcome of the event. In addition to the AE categories listed below, AEs will be listed as “Early,” within 30 days of surgery, or “Late,” more than 30 days after surgery. The investigator will follow each subject who experiences an AE until the event resolves. In the unusual circumstance that an AE has not resolved by the time of the subject’s completion of the study, an explanation will be entered on the appropriate eCRF.

Anticipated adverse events, as described in the coflex IFU, are:

<u>Adverse events that are associated with any surgery include:</u>

- Infection (deep or shallow)
- Pneumonia (lung infection)
- Atelectasis (collapsed lung)
- Septicemia (blood poisoning)
- Injury to blood vessels
- Soft tissue damage
- Phlebitis (inflammation of the blood vessel in your leg
- Thromboembolus (blood clot in legs) or pulmonary embolism (blood clot in lung)
- Hemorrhage (excessive bleeding)
- Respiratory distress (difficulty breathing)
- Pulmonary edema (abnormal collection of fluid in lungs)
- Reactions to the drugs or anesthetic agent used during and after surgery
- Reactions to transfused blood

- Failure of the tissue to heal properly (e.g., hematoma [a pocket of blood cause by bleeding from a broken blood vessel]; seroma [buildup of clear body fluid in the tissue]; dehiscence [failure of the incision to completely heal which may allow it to reopen], etc.) which may require drainage, aspiration (removing a substance using suction); debridement (surgery to clean foreign material and dead tissue out of a wound); or other intervention
- Incisional pain
- Heart attack
- Stroke
- Death

Adverse events that are associated with decompression:

- Damage to nerves leading to sensory or motor deficits (changes in the sensation and/or muscle weakness in your legs)
- Paralysis (loss of ability to move muscles with the loss of feeling also)
- Parethesias (a sensation of pricking, tingling, or creeping on the skin)
- Cauda equina syndrome (severe nerve compression cutting off sensation and movement to your legs with possible loss of bowel and bladder function)Damage to nerves, blood vessels, and nearby tissues including, for example, muscle and/or ligament injury
- Epidural bleeding (bleeding around the membrane covering the tissue surrounding your spinal cord that may require a blood transfusion or another operation)
- Epidural hematoma (a pocket of blood caused by a broken blood vessel or bone bleeding in the membrane covering the nerves or the tissues surrounding your spinal cord)
- Epidural fibrosis (scar tissue formation on the membrane covering the nerves)
- Instability of the operated or adjacent vertebrae
- Blindness by prolonged pressure on the eye during the operation
- Osteolysis
- Injury to the spinal cord or the nerves leaving or entering the spinal cord
- Loss of the ability to control bowel or bladder function)
- Retrograde (reverse) ejaculation, sexual dysfunction, or possible sterility
- Disc herniation (“slipped disc”)
- Injury to blood vessels
- Dural violation, with or without reaction (injury of the membrane [dura] surrounding the spinal nerves which may or may not result in leakage of spinal fluid)
- Impaired muscle or nerve function
- Hemorrhage (excessive bleeding)
- Epidural injection reaction
- Epidural injection failure
- Fracture of the vertebrae, spinous process (the part of your spine that you can feel through the skin on your back), or other damage to bony structures during or after surgery
- Postoperative muscle and tissue pain
- The chance that the surgery will not reduce the pain or symptoms felt before the surgery
- Spontaneous fusion (unplanned, self-generated fusion of the vertebra)
- The spine may undergo unfavorable changes or deterioration at the operated level(s) and/or the levels above and below including loss of proper spinal curvature, correction, height, and/or reduction, or malalignment, which may require another surgery

Adverse events that are associated with coflex implant:

- Implant malposition or orientation (the implant could be improperly positioned)
- Allergies to implant materials (possible allergic reaction to the metal)

- Possible wear debris (there may be some wearing of the implant material against bone or another part of the implant that creates very small particles; it is possible that these particles may eventually cause the local tissues such as bone, nerves and nearby soft tissue to respond badly)
- Impantation of the study device at the wrong level of the spine
- Fracture of the vertebrae, spinous process, or other damage to bony structures during or after surgery
- Implant may loosen, deform (permanently change shape), break, fatigue (wear out), or move which may require another surgery to correct the problem and/or remove the implant
- Instruments also may break or malfunction in use, which may cause damage to the operative site or adjacent structures

6.2. Assessment of Severity:

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

6.3. Relationship to Device / Procedure

The investigator will evaluate the relationship of the adverse event to the research intervention according to the following definitions. The term "device-related," as it pertains to adverse events, means that the event was or may have been attributable to a device, or that a device was or may have been a factor in an event, including those occurring as a result of malfunction, poor manufacture, inadequate labeling, or improper design.

The term "procedure-related," as it pertains to adverse events, means that the event was or may have been attributable to a procedure, or that a procedure was or may have been a factor in an event.

- **Definite**
  The adverse event is clearly related to the investigational agent(s) or research intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, or is otherwise logically related to the investigational product, and no alternative cause is present.
- **Probable**
  The adverse event is likely related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, or is otherwise logically related to the investigational product, but an alternative cause may be present.
- **Possible**
  The adverse event may be related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational

agent(s) or research intervention, follows a suspected pattern of response, or is otherwise logically related to the investigational product, but an alternative cause is present.

- **Unlikely**
  The adverse event is doubtfully related to the investigational agent(s) or intervention: the adverse event has a temporal or other relationship to the administration of the investigational agent(s) or research intervention, but follows no known or suspected pattern of response, and an alternative cause is present.
- **Not Related**
  The adverse event is clearly NOT related to the investigational agent(s) or intervention: the adverse event has no temporal or other relationship to the administration of the investigational agent(s) or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

6.4. Serious Adverse Events

A serious adverse event (SAE) is any adverse event that:

- Results in death;
- Is life-threatening; the subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient;
- Results in hospitalization (initial or prolonged);
- Results in disability or permanent damage; the event resulted in a substantial disruption of the person's ability to conduct normal life functions;
- Results in a congenital anamoly or birth defect;
- Requires intervention to prevent permanent impairment or damage; medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure.
- Results in any other serious, important medical events; the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes.

In case of Serious Adverse Events (SAE), the Investigator must notify the CRO as soon as possible but at least within **one working day** after becoming known to the Investigator, by entering the data in the Electronic Data Capture (EDC) system.

The first report of a SAE must be completed within one working day after becoming known to the Investigator by completing in full the Adverse Event eCRF, i.e., subject's initials, date of evaluation, subject's ID, surgeon's name, visit type, onset date, severity of event, relationship to device, relationship to procedure and event classification. The report of a SAE by EDC will alert the clinical trial manager at MCRA via e-mail once the eCRF has been submitted via Electronic Data Capture (EDC).

If for some reason, the EDC system is not accessible, the SAE notification may be submitted via email to SAE@mcra.com. The email should include the Investigator's name, subject's ID, and a description of the event. This notification method should only be used if the EDC data entry cannot be completed within the specified time requirement (i.e., 1 working day). As soon as the EDC system is available, the Adverse Event eCRF should be completed.

New SAEs will only be documented for each patient until the last study related patient visit.

MDRs have to be reported within 30 working days. In case of acute risk the incident has to be reported immediately.

6.4.1. Serious Device-Related Adverse Events

In the coflex cohort: presence of a major device-related adverse event is defined as an event simultaneously having a severity rating of 'Serious" and a device relatedness of 'Definitely'. In the control cohort, since there is no device, this endpoint will be identified as any serious AE that is classified as definitely related to surgery.

6.5. Unanticipated Adverse Device Effect (UADE)

An UADE is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subject." AEs that might reasonably occur because of placement or attempted placement of the investigational product or during follow-up were identified through a risk analysis. The Risk Analysis lists clinical risks to the subject associated with study participation.

If Paradigm Spine determines that UADE of an investigational device presents an unreasonable risk to study subjects, Paradigm Spine/physician will:

- terminate the investigation, or the parts of the investigation presenting that risk, within 5 working days after Paradigm Spine makes an "unreasonable risk" determination or within 15 working days after Paradigm Spine first received notice of the UADE,
- immediately investigate and evaluate the adverse effect (21 C.F.R. § 812.46(b)(1) and (2)),
- report the results of the investigation to all reviewing IRBs and to all participating investigators within 10 working days after Paradigm Spine first receives notice of the UADE (21 C.F.R. § 812.150(b)(1)),
- resume the study, if appropriate, as specified by the IRB.
- notify FDA of event and any action taken by Paradigm Spine as a result of this UADE.

6.6. Event Reporting:

The FDA's Medical Device Reporting requirements regulations state the following requirements for event reporting:

MDR Mandatory Reporting Requirements:

Manufacturers: are required to report to FDA when they learn one of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to FDA when they become aware that one of their devices has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction happened again. Deaths, serious injuries and malfunctions must be reported to FDA within 30 calendar days from the manufacturer becoming aware of an event. Use FDA form 3500A.

Events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other types of events within 5 work days from becoming aware of an event. Use FDA Form 3500A.

User Facilities: User Facilities (e.g., hospitals, nursing homes) are required to report a suspected medical device-related death to both the FDA and the manufacturer. User facilities should report a medical device-related serious injury only to the manufacturer. If the medical device manufacturer is unknown, the user facility should report the serious injury to FDA. A user facility is not required by the MDR regulation to report a malfunction, but can use the voluntary MedWatch program to advise FDA of problems with medical devices. Health-care professionals within a user-facility should familiarize themselves with their institution's procedures for reporting adverse events to the FDA. See "Medical Device Reporting for User Facilities", a guidance document issued by FDA.

In this trial all SAEs reported by the investigators will be evaluated but only MDRs will be reported to the FDA by the sponsor.

6.7. Documentation of Adverse Events

New or worsening AEs will only be documented for each patient until the last study related patient visit.

The investigator will assess and record any AE in detail on the 'AE' form included in the case report forms (eCRFs).

Investigators will actively check for and report potential device- or procedure- related Adverse Events for all study patients in the time period between the first device application and the end of the clinical phase of the trial at the site.

Investigators will also report to the CRA all unexpected (i.e., not listed in Section 6.1) and Serious Adverse Events (see Section 6.4 for contact information) by completing the Adverse Event eCRF in the EDC. The CRA will forward this report to the sponsor. The sponsor will then make an evaluation if he agrees that the unexpected and serious AE was in fact device- or procedure-related. It is the reporting responsibility of the Investigator to notify the responsible IRB of Adverse Events which are classified by the sponsor as serious, unexpected and related, unless otherwise required and documented by the IRB.

All AEs must be recorded and followed up until the event is either resolved or adequately explained, even after the patient has completed the clinical investigation.

7. Statistical Analysis

7.1. Accounting for Non-Randomized Treatment Group Comparisons

This study design includes concurrently enrolled, but non-randomized investigational and control arms. Covariate balance will be achieved using sub classification based on propensity score (PS) quintiles. The PS subclasses will be determined by an outcomes-blinded statistician soon after prospective enrollment is completed and before most if not all patients are evaluable for the two-year effectiveness endpoint. The process of assigning patients to subclasses will be submitted to FDA for review and acceptance prior to unblinding of the PS statistician. Selection into a PS subclass is the observational study equivalent to randomization. Subclasses will be determined using methods summarized below to ensure that within subclass, groups are well balanced for a rich set of clinically relevant baseline covariates. Analyses will proceed as if patients were

randomized to treatment group within subclass and effectiveness outcomes will be compared between groups using methods that account for PS subclass. There is a compelling case to be made that informative prior Bayesian designs are especially appropriate for post approval studies (PAS) since recent rigorous objective data is available. To make use of this prior information, a Bayesian design with informative priors has been specified for each Objective. For these Objectives, patient-level data from the IDE study are used to formulate the PAS prior distributions.

To make use of the beta-binomial updating from prior to posterior it is necessary to have counts of the numbers of successes and failures observed among the prospectively enrolled patients for both groups. These counts are added to prior beta distribution parameters that reflect (what amounts to) the prior numbers of success and failures. Combined, these sums of successes and failures determine the Bayesian posterior distribution. The simplicity of this approach stems from the mathematical convenience of conjugate priors which have, in addition to computational convenience, the practical advantage of being interpreted as additional data (Gelman, 2014)[12]. However, the numbers of successes and failures observed from each group to be used to update the prior distribution must account for the propensity subclass design.

The following approach will be used to determine adjusted numbers of successes and failures that account for the relative contribution of each PS subclass. This approach is necessary to produce results that take advantage of the covariate balance achieved through PS sub classification. We first consider how this would be done if there was no missing data. This is the approach that will be used in sensitivity analyses involving the several completers analysis sets defined primarily across time. The section below concerning missing data shows how missing data will be incorporated in the primary determination of the Bayesian probability of superiority and non-inferiority.

To adjust for PS subclass, the average success rate over the 5 subclasses will be computed for each treatment group. This is to allow each quintile subclass to contribute equally to the estimated success rates. Consequently, the covariate balance is preserved in the final estimates of CCS probabilities. By equally weighting the PS subclasses, the results become estimates of expected values under the assumption of randomized treatment assignment within PS subclass. Under this assumption, we would expect approximately the same number of investigational and control patients within each subclass implying the equality of weights. The PS adjusted failure probability for each group will be computed as one minus the adjusted success probability.

If the crude numbers of success and failures were used to update the priors, imbalance in the numbers of investigational and control subjects within subclasses would clearly result in a biased treatment effect estimate whenever overall success rates differed among PS subclasses.

By combining the subclass success probabilities in this way, the weights given to each subclass contribution when determining the total numbers of successes and failures used to update the prior are the same for both groups.

The PS subclass adjusted success and failure probabilities will be multiplied by the total treatment group specific sample sizes (across all subclasses) to determine PS subclass adjusted numbers of successes and failures for each group. The adjusted numbers of success and failures in each group will be added to the group specific beta distribution parameters to update the prior

12 Gelman, A. (2014). *Bayesian data analysis* (Third edition. ed.). Boca Raton: CRC Press.

distributions and determine the posterior distribution of the group differences in success probability.

The theoretical justification for this approach arises from causal analysis concepts. In causal analyses that use propensity score subclassification, Average Treatment Effect (ATE) is determined as the within subclass total sample size weighted average of subclass specific effect sizes. The proposed strategy is consistent with how ATE estimates of relative effectiveness are determined.

7.2. Analysis Sets

The following analysis sets are defined.
Intent-to-treat analysis set – Propensity Score Selected (ITT–PS Selected): The ITT–PS Selected analysis set will include all subjects assigned to either the study or control groups in which treatment was attempted as defined by the recording of incision time. Subjects will be classified by the group in which they are assigned, regardless of whether or not that treatment was actually completed. Intraoperative failures will be included in primary non-inferiority testing as composite clinical endpoint failures. Primary efficacy analyses will be conducted using the ITT–PS Selected analysis set. A subject must be selected into a PS subclass in order to be included in analyses. The PS subclassification procedure is designed to retain all subjects receiving the study device, if possible. Since selection into a PS subclass is the observational study equivalent to randomization in a randomized study, control subjects not selected into a PS subclass will not be included in the ITT–PS Selected analysis set and not included in primary effectiveness and safety analyses. Safety data will be summarized separately for trimmed controls.

Completers Analysis Sets: Completers analysis sets will be defined at ITT–PS Selected evaluable for composite clinical success.

***Safety analysis set*:** The Safety analysis set will include all subjects in the ITT–PS Selected analysis set plus study device patients who were not selected into a PS subclass, if any. Study device patients who were not selected into a PS subclass will be assigned to the subclass with the largest propensity scores for analyses that control for PS. Primary safety analyses will be conducted using the Safety analysis set.

Per Protocol analysis set (PP): The PP analysis set will include subjects in the ITT–PS Selected analysis set with no major protocol violations of inclusion or exclusion criteria, as determined by the Clinical Events Committee (CEC) and who are evaluable for the Month 24 composite clinical success endpoint (Objective 2, 3, and 4) or evaluable for the Month 60 CCS (Objective 1). It may also exclude subjects with confounding medical events or treatments following index surgery that are expected bias determination of the primary composite clinical success endpoint, as determined by the CEC. Secondary efficacy analyses will be conducted using the PP analysis set.

7.3. Objective 1: 5-Year Superiority

Five-year superiority will be evaluated by testing the hypothesis that the coflex device in conjunction with surgical decompression is superior to decompression alone at five years. This objective will be met by testing the following superiority hypotheses:

Ho: $CCS_{coflex+decomp.} - CCS_{decomp} \leq 0$ (not superior)
Ha: $CCS_{coflex+decomp.} - CCS_{decomp} > 0$ (superior)

An informative prior based on final 5-year IDE study results for the coflex group will be used as described below. A non-informative prior will be used for the decompression alone group. The Bayesian posterior probability that ($\mathbf{CCS_{coflex+decomp.} - CCS_{decomp}) > 0}$ will be determined.

If the posterior probability is ≥ 0.95 then superiority will be concluded.

7.4. Objective 2: 2-Year Non-Inferiority

Two-year non-inferiority will be evaluated by comparing clinical status of patients implanted with the coflex® device in conjunction with surgical decompression relative to surgical decompression alone at two years post operatively by confirming clinical non-inferiority in terms of Month 24 composite clinical success (CCS) defined similarly to the IDE study endpoint. To meet this objective, the following hypotheses will be tested:

Ho: $CCS_{coflex+decomp.} - CCS_{decomp} \leq -0.10$ (inferior)
Ha: $CCS_{coflex+decomp.} - CCS_{decomp} > -0.10$ (not inferior)

Non-inferiority will be concluded if the posterior probability is at least equal to 0.95.

7.5. Objective 3: 2-Year Superiority

If 2-year non-inferiority is demonstrated, the following superiority hypotheses will be tested.

Ha: ($CCS_{coflex+decomp.} - CCS_{decomp}$) ≤ 0.
Ha: ($CCS_{coflex+decomp.} - CCS_{decomp}$) > 0.

This will be done by determining the Bayesian posterior probability that **($CCS_{coflex+decomp.} - CCS_{decomp}$)** > 0. The same informative prior for the coflex® group only will be used. If the posterior probability is ≥ 0.95 then superiority will be concluded.

7.6. Objective 4: Real Conditions of Use

Coflex device performance will be evaluated in a "real conditions of use" study by testing the hypothesis that device performance is not clinically inferior in the PAS population relative to device performance defined by IDE study results. Patients will be enrolled from sites that were not involved in the IDE study. The same Month 24 composite clinical success (CCS) endpoint used in the IDE trial will be used in analyses to facilitate this comparison.

Ho: $CCS_{PAS} \leq 0.662 - 0.10 = -0.562$ (inferior)
Ha: $CCS_{PAS} > 0.662 - 0.10 = -0.562$ (not inferior).

Non-inferiority will be concluded if the posterior probability is at least equal to 0.95.

If the inferiority hypothesis is rejected, then the numbers of coflex® successes and failures observed in the PAS will be used to update the Bayesian posterior probabilities of non-inferiority and superiority relative to fusion that were first established in the IDE study and reported in the coflex® SSED. This will facilitate a formal accumulation and summary of what has been learned about the relative effectiveness of coflex® compared to fusion based on pooling relevant information from the IDE trial and this PAS. As reported in the coflex® SSED, the Bayesian posterior probability that coflex® is not clinically inferior to fusion (δ=-0.10) is 0.999362. Similarly, the Bayesian posterior probability that coflex® is superior to fusion in terms of Month 24 CCS was reported to be equal to 0.927550.

7.7. Sample Size Analysis

Details concerning the Bayesian simulations for this study were previously reviewed (**Bayesian Simulations Memo, Version 4.1, May 5, 2015**).

7.7.1. Objective 1: 5-Year Superiority

These simulations were used to evaluate the power and type 1 error for determining superiority of coflex in conjunction with surgical decompression relative to surgical decompression alone at Month 60. For the purpose of these simulations it was assumed that the Month 60 success rate would be 0.57 for coflex®. The prior distribution derived in the Memo is beta(82.1,62.1) reflecting a 20% ,discount off of a total prior sample size of N=179. Power was found to be equal to 83% if the true superiority margin is 12.5%. If the true superiority margin is only 10%, then power to conclude superiority is reduced to 65%. Type 1 error was determined through simulation by assuming that the probabilities of Month 60 success were equal to 0.57 for both treatment groups. The estimated type 1 error rate is equal to 0.037(SD=0.0011) based on an average of 10 identical simulations with varying randomization seeds.

It may be now be noted that subsequent to the Bayesian design memo submission, the final results from the PMA study were submitted to FDA in the Final Report (P110008/R014). The Month 60 PAS CCS was achieved in 55.9% (104/186) patients which is very close to the projected success rate of 57%. The total sample size of 186 is slightly larger than the assumed 179 which implies a discount of the prior of 23% rather than 20%. Sensitivity analyses (see Table 4 from Bayesian Memo) were provided that demonstrate that type 1 error is 0.040, still below 0.05, if the true success rate is 56% rather than 57%.

7.7.2. Objective 2: 2-Year Non-Inferiority

Bayesian simulations were performed to evaluate the operating characteristics for testing the Objective 2 non-inferiority hypothesis. In the pivotal IDE study, 135 of 204 patients (66.2%) achieved Month 24 CCS. These results were used to define the prior distribution for coflex® in conjunction with surgical decompression as beta (135.5, 69.5) since the distribution prior to the IDE trial was specified as beta (0.5, 0.5). This Jeffries non-informative prior was assumed for patients undergoing decompression alone. A non-inferiority margin of -0.10 is specified. Non-inferiority will be concluded if the Bayesian posterior probability that (**$CCS_{coflex+decomp.} - CCS_{decomp}$) > -0.10** is at least equal to 0.95. When evaluating statistical power, it was assumed that the true success rate 0.662 for patients treated with coflex®. However, preliminary results from the German decompression study suggest some an advantage of coflex® over decompression alone. Therefore, when evaluating power, Month 24 CCS for decompression alone was assumed to be at least 2% lower, or 0.642. In contrast, Type 1 error was evaluated by assuming that the coflex® success rate 0.662 but that the success rate for decompression was 0.10 larger. With N=150 patients per group, power was shown to be 89%; and type 1 error was shown to be 0.042 and 0.052 'prior to the prior' and with the prior engaged, respectively.

7.7.3. Objective 3: 2-Year Superiority

Superiority of coflex in conjunction surgical decompression relative to decompression alone will be evaluated by determining the Bayesian posterior probability that (**$CCS_{coflex+decomp.} - CCS_{decomp}$) > 0.** Ho will be rejected in favor of Ha if the Bayesian posterior probability is at least equal to 0.95. The same prior distributions that were used in Objective 2 will be used in the evaluation of this posterior probability. The expected device group difference in Month 24 CCS between coflex® and decompression alone was evaluated based on results from an administrative analysis of the ongoing PAS being conducted in Germany. This study is also comparing coflex in conjunction with surgical decompression relative to surgical decompression alone. This analysis included 74

and 79 patients, respectively, in the coflex and decompression arms which comprised 85% and 81% of patients theoretically due for Month 24 follow-up. The device group difference in Month 24 overall success was 12.5% (95% CI -3.5% to 28.4%) based on a simplified CCS that incorporated reoperations, lumbar injections, and ODI improvements. Bayesian simulations demonstrate that with N=150 patients per group, there is 88% statistical power to demonstrate superiority. Type 1 error is controlled at <0.05 prior to prior and with prior on coflex® engaged. If the true difference is only 10%, then power is reduced to 73%.

It may be now noted that subsequent to the Bayesian design memo, the final results from this study have been published[13] including a Month 24 CCS designed to be similar to the US IDE Study. Results demonstrated a 16.7% superiority margin (95% CI 3.1% to 30.2%) with coflex and decompression composite success observed in 58.4% (59/101) and 41.7% (43/103) patients, respectively.

7.7.4. Objective 4: Real Conditions of Use

Non-informative priors were assumed for the both copmarisons groups, since IDE results cannot be used as the basis of an informative prior if the comparison is to be made to that same IDE trial. However, the Bayesian simulation R function was modified to reflect that it is known that exactly 135 successes were observed among 204 evaluable patients in the coflex IDE analysis set (see Simulation Report, Section 8.3). Otherwise, all other features of the Bayesian simulation were kept the same.

A design was identified that uses a non-inferiority margin of -0.1175 and a 0.95 posterior probability threshold. This design has an estimated type 1 error that of 0.045 and power of about 80%. Other assumptions include expected success rates 0.662 in both groups when determining power and assuming that the Month 24 success rate in the PAS population is 0.10 smaller than in the IDE study population for evaluating type 1 error.

7.8. Alternative CCS Using Treadmill Test

Objectives 1, 2 and 3 focus on comparisons between coflex® in conjunction with surgical decompression relative to decompression alone. A modified CCS will be assessed as a secondary endpoint for these objectives. For this modified CCS, the criterion that the Oswestry Disability Index (ODI) must improve by at least 15 points will be replaced by a criterion that more directly measures physical function. This endpoint (CCS-WDT) is a function of the maximum time a patient can walk on a treadmill (up to 15 minutes) before symptoms are too severe to continue. The specific treadmill success criterion will be an improvement in the total walking time from baseline to follow-up of at least 8 minutes. For patients with a baseline value that is >7 minutes, the follow-up walking test success criteria is the ability to achieve the maximum walking test time of 15 minutes. This allows patients with >7 minutes at baseline to achieve success. These definitions were developed using data from the ongoing German study of coflex® compared to decompression alone.

7.9. Analysis of Secondary Effectiveness Endpoints

Secondary continuous effectiveness endpoints will be summarized by treatment group over time and as changes over time with descriptive statistics including means, standard deviations,

13 Schmidt S, Franke J, Raushmann M, Adelt D, Bonsanto MM, Sola S. European Study of Coflex and Decompression Alone. Prospective, Randomized, Controlled, Multicenter Study With Two-year Follow-up to Compare the Performance of Decompression With and Without Interlaminar. Journal of Neurosurgery: Spine. EPub ahead of print, Jan 26, 2018.

median, minimum and maximum values. Secondary categorical effectiveness endpoints will be summarized by treatment group over time using counts and percentages. Descriptive effect size measures such as mean differences and differences in percentages responding will be provided with 95% confidence intervals or 95% credible intervals as an aid in evaluating the likely ranges of true treatment group differences.

7.10. Follow-Up Compliance

Follow-up compliance will be determined separately by device group on the basis of theoretical due and expected due as illustrated in FDA Guidance (2004)[14]. Separate compliance estimates for composite clinical success, and for clinical indices (i.e., ODI) will be provided over time.

7.11. Handling of Missing Data for Primary CCS Endpoints

7.11.1. Bayesian Multiple Imputation

To best preserve an intent-to-treat analysis, the testing of the primary Month 60 supeiority hypothesis (Objective 1) will per be done on the ITT–PS selected analysis set. Those subjects who withdraw, or who are lost to follow-up (LTFU) after enrollment will be included in the analysis using a modification of Bayesian multiple imputation to accomodate the PS subclass design. This analysis will be the primary analysis, but recognizing that there is no way, statistically, to handle these subjects without possibly introducing bias, a tipping point analysis will be also be conducted. For comparison purposes, a completers analysis will also be performed. The following describes the method. A similar method will be applied to analyses for other objectives.

In general, Bayesian Multiple Imputation (MI) may be employed to impute the expected status at Month 60 for patients who have not completed follow-up and have not been identified as “terminal failures”. Terminal failures include any event which is counted as a CCS failure no matter what happens after such an event occurs such as a secondary surgical invention. The imputation algorithm uses a beta-binomial distribution to model the transition probabilities from the outcome at month j to that at month 60, separately for the treatment and control groups. Specifically, the probability of a success for a subject in treatment group t, with last follow-up j and last follow-up value r can be described using a beta distribution:

$$\Pi_{p,t,j,r} \sim \beta(1 + S_{p,t,j,r} , 1 + F_{p,t,j,r})$$

Where p = propensity score subclass = {1, 2, 3, 4, 5}

t = treatment group = {coflex=S, Decompression=D}

j = follow-up time = {3, 6, 12, 24, 36, 48}

r = success or failure status at time j = {1=success, 0=failure}

$\Pi_{p,t,j,r}$ = Month 60 success probability for subjects in subclass p, in treatment group t, who were successes (r=1) or failures (r=0) at follow-up time j.

$S_{p,t,j,r}$ = Number of Month 60 successes for subjects in subclass p, in treatment group t, who were successes (r=1) or failures (r=0) at follow-up time j.

14 Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications Document issued on: December 2, 2004.

$F_{p,t,j,r}$ = Number of Month 60 failures for subjects in subclass p, in treatment group t, who were successes (r=1) or failures (r=0) at follow-up time j.

Note that these transition beta distributions assume non-informative prior distributions to allow only the observed data to impact on the multiple imputations (i.e., all a and b are set to 1). Subsequently, the informative prior on the study device group is applied to determine the posterior distribution of non-inferiority.

In order to implement the Bayesian Multiple Imputation algorithm, the following steps will be used.

1. For each patient that has not completed follow-up, a value π_i is randomly chosen from $\Pi_{p,t,j,r} \sim \beta(1 + S_{p,t,j,r}, 1 + F_{p,t,j,r})$ corresponding to their PS subclass, treatment group, and success-failure status at their last known follow-up; this value represents the probability that the subject is a success at 60-months.

2. Using this randomly chosen π_i, the patient is then assigned a success (1) or failure (0) from a random draw of the binomial distribution *Bin(n,p)* with $n = 1$ and $p = \pi_i$.

3. Steps 1-2 are repeated for all subjects with incomplete follow-up, separately for each treatment group and propensity score subclass.

4. Using the resulting completed datasets (containing both observed and imputed values at month 60), the PS-adjusted total number of successes (S_t) and failures (F_t) at month 60 are calculated for each treatment group using the average of PS subclasses as described above. The probability of success for each treatment is then chosen randomly from the resulting posterior beta distributions incorporating the informative prior in the study device group and the non-informative prior for controls. The distribution of the difference in success probabilities is therefore:

$$\pi_S - \pi_D \sim \beta(82.1 + S_S, 62.1 + F_S) - \beta(1 + S_D, 1 + F_D)$$

5. Step 4 is repeated (n = 10,000 times), to obtain the posterior distribution of the differences in treatment success ($\pi_S - \pi_D$), and the posterior probability of non-inferiority is calculated as the proportion of times that $\pi_S - \pi_D \geq -\delta$.

6. To complete the multiple imputation and obtain the final posterior non-inferiority probabilities, steps 1-5 are repeated 20 times and the final posterior probability is determined as the average of the 20 multiple imputations.

7.11.2. Tipping Point Analysis for Primary Outcomes

A tipping point sensitivity analysis will be conducted in which missing values in each group are separately assumed to be either successes or failures. Treatment group differences will be computed based on all possible combinations of assigning success or failure to the primary overall success endpoint to the patients in the two groups. For example, one scenario will be that all missing coflex device observations are failures and all missing decompression alone observations are successes. The next scenario would have one success and the remaining missing values as failure for coflex and all missing controls as successes. For each objective, the Bayesian posterior probability will be determined. These results will be plotted using a dot plot with the number of missing assumed as failures for coflex in conjunction with surgical decompression on the x-axis and the number of missing assumed as failures for controls on the Y-axis. The dots will be color

coded to indicate whether or not the primary statistical conclusion changes under each individual scenario. If the fraction of scenarios in which the statistical conclusion changes is small, the primary results will have been shown to be robust against assumptions concerning missingness.

7.11.3. Plan for Missing Baseline Covariates

Since data for the study device patients and control group patients will be prospectively collected, it is anticipated that there will be very little, if any missing covariate data. If there are some missing covariate values, and these represent a very small percentage of the total amount of covariate information overall and for every subject, then the missing data will be imputed using a single imputation strategy employing multiple linear regression for continuous covariates and multiple logistic regression for dichotomous covariates. These models will include all other variables to be used in the PS modeling. If there is more than a trivial amount of missing covariate data, then a multiple imputation strategy will be used. The multiple imputation strategy will involve determining PS scores for each of 20 MI completed data sets and then using the average PS score for each step in the PS subclassification identification strategy. If MI is needed, it is likely that the missing value pattern will not be monotonic. Therefore, a fully conditional specification (FCS) approach will be utilized as implemented in SAS Proc MI. Details regarding the imputation strategy, if needed, will be included in the PS Results Memo to be submitted for FDA review prior to unblinding outcomes to the outcomes-blinded statistician responsible for determining the PS subclasses.

7.12. Sub Group Analysis

Primary endpoints and selected secondary endpoints will be subjected to stratified analyses in order to evaluate poolability and heterogeneity of treatment group differences. Stratifications will include age (<65 vs ≥ 65 years), gender, body mass index (<30 vs ≥ 30 k/m^2) and other clinically relevant factors.

7.13. Device Survival through 24 months

Kaplan-Meier survival analysis[15] will be used to characterize and compare treatment failure time distributions between. Life-tables will be tabulated indicating the number of “failures” and the number of “at-risk” patients over time for each endpoint, separately by device group.

7.14. Alternative and Incremental Composite Clinical Success

Secondary analyses may also involve device group comparison on the basis of “alternative and incremental composite clinical success endpoints” in order to provide a richer assessment of the multi-factorial treatment response using the approach recently described by Bae, Lauryssen, Maislin et al (2015)[16]. Incremental composite endpoints are constructed by adding additional success criteria. An example of this is the addition of the requirement that there is no Month 24 oral narcotics (opioids and opiates) use. This variable will be evaluated as an outcome variable alone and as part of the incremental CCS analyses.

15 Kaplan EL and Meier P. Nonparametric estimation from incomplete observations, Journal of the American Statistical Association, 53:457-481, 1959.

16 Bae WH, Lauryssen C, Maislin G, Leary S, Musacchio MJ. Therapeutic sustainability and durability of coflex® interlaminar stabilization after decompression for lumbar spinal stenosis: a four year assessment. *International Journal of Spine Surgery 2015* http://ijssurgery.com/10.14444/2015

7.15. Risk Factor Analysis

Logistic regression analysis[17] may be used to assess potential factors associated with success or failure of the investigational device including age, gender, BMI, and baseline ODI.

7.16. Site Poolability

Given that this is a concurrent enrollment study and that sites will enroll only into one of the treatment groups, site heterogeneity in relative effectiveness cannot be evaluated. Instead, site-to-site variability will be evaluated for each treatment arm separately. This will be done using a random effects meta-analysis approach using the R package ***metafor*** to implement the analysis. True effects are assumed to be normally distributed with mean μ and variance σ^2. An arcsine variance stabilizing transformation will be utilized to make the data amenable to random effects modelling. By imposing a specified distribution on the site-to-site variability, i.e. a normal distribution with mean m and variance t^2, sensitivity to small sample sizes in individual sites is reduced and the parameters reflecting the magnitude of site-to-site variability are naturally derived. The quantitative measure of the magnitude of heterogeneity is I^2. I^2 is the fraction of t^2 that is due to effect size heterogeneity, as opposed to sampling variance. Fractions 25% and less are considered small. .

7.17. Design and Conduct of Observational Study

7.17.1. Propensity Score Analysis

The study design includes concurrently enrolled, but non-randomized investigational and control arms. Subjects groups will also be comparable with regard to timing of treatment owing to concurrent enrollment. Propensity score subclassification (Rosenbaum and Rubin, 1983)[18] will be used to addresses potential selection bias inherent in non-randomized comparisons. The PS model will be evaluated according to rigorous criteria (Imbens and Rubin 2015)[19] using a published heuristic (Maislin and Rubin 2010)[20]. Applications of this heuristic have been recently been published (e.g., Keenan, Maislin, et al 2014[21]. Arnardottir, Lim, Keenan, Maislin et al 2014[22]; and Pak, Keenan, Jackson, Grandner, Maislin et al 2014[23]). The heuristic is designed to identify 5 sub classes in which the groups to be compared share the same multivariate distribution of a comprehensive set of baseline variables. Within each sub class, patients are therefore equally likely to have received the investigational device or control. The primary treatment comparison will be based on PS-quintile stratified analyses.

The propensity score is the observational study analogue of complete randomization in randomized experiments in the sense that its use is not intended to increase precision but only to

17 Hosmer DW and Lemeshow S. Applied Logistic Regression. New York: John Wiley & Sons, 1989.
18 Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. Biometrika. 1983;70(1):41-55.
19 Imbens G, Rubin DB. Causal inference for statistics, social, and biomedical sciences: an introduction. New York: Cambridge University Press; 2015.
20 Maislin G, Rubin DB. Design of Non-Randomized Medical Device Trials Based on Sub-Classification Using Propensity Score Quintiles. American Statistical Association Joint Statistical Meetings 2010; Vancouver, Canada.
21 Keenan BT, Maislin G, Sunwoo BY, et al. Obstructive sleep apnoea treatment and fasting lipids: a comparative effectiveness study. Eur Respir J. 2014;44(2):405-414.
22 Arnardottir ES, Lim DC, Keenan BT, et al. Effects of obesity on the association between long-term sleep apnea treatment and changes in interleukin-6 levels: the Icelandic Sleep Apnea Cohort. J Sleep Res. 2015;24(2):148-159.
23 Pak VM, Keenan BT, Jackson N, et al. Adhesion molecule increases in sleep apnea: beneficial effect of positive airway pressure and moderation by obesity. Int J Obes (Lond). 2015;39(3):472-479.

eliminate systematic biases in treatment-control comparisons (Rubin 2008)[24]. Moreover, the "propensity score technique allows the straightforward assessment [of] whether the treatment groups overlap enough regarding baseline covariates to allow for a sensible treatment comparison" (Yue 2007)[25].

The PS sub classes will be formed when the prospective enrollment is completed. As part of the modeling process it typically is necessary to iteratively trim subjects from the extremes of the PS distributions in order for the Imbens and Rubin 2015 PS model estimation validity criteria to be met. For regulatory studies, the heuristic has been modified to initially force retention of all investigational device subjects. If it is not possible to meet the optimality criteria when retaining all study device subjects, only then will we sequentially trim a (very) small number of investigational patients in an attempt to satisfy the optimality criteria. These processes will all be detailed in a PS Results Memorandum that will be submitted to FDA for review prior to unblinding of the outcomes-blinded statistician responsible for identifying the optimal PS subclassification. In the event it is necessary to exclude any investigational device subjects, effectiveness results for these subjects will be summarized separately, and compared to those in the primary analysis set, and the potential implications of excluding patients discussed in the PMA. These patients will, however, be included in all safety analsyes. In safety comparisons that adjust for PS subclass, excluded study device patients will be included in the quintile with the highest propensity scores. Non-selected control patients will be not be included in efficacy analyses. Safety events for non-included controls will be listed separately.

It is important to emphasize that the sequential model building process used to identify an analysis data set for which there is adequate covariate balance within subclasses` poses no concern for Type I error inflation. This is because the PS model building process makes no use of outcome data. To avoid bias, a separate statistician without access to outcome data will form the PS sub classes through the model identification process described in [Maislin and Rubin 2011]. This sequential model-building heuristic should be viewed as part of the 'design of the observational study'. Here 'design' may be interpreted as "contemplating, collecting, organizing, and analyzing of data that takes place prior to seeing any outcome data (Rubin 2008)[24]". At its conclusion, verification of balance between device groups within sub class will be done through graphical as well as through analytical means.

Given the expected similarity of the populations from which the investigational and control groups are to be obtained and the specificity of the clinical indication, it is expected that no more than 20% of controls will be trimmed. The control sample size has been adjusted upwards by 20% to account for this. The sample size for the investigational device has been adjusted upwards by 5% just in case trimming of a small number of subjects from the investigational device group is required in order to identify sub classes that meet the Rubin criteria for PS model validity.

It is acknowledged that the proposed propensity score design can only assess the comparability of the two groups after enrollment is complete. This raises the risk that at the end of planned enrollment, the analysis sets may not be adequately balanced given the available patients. If needed, this risk can be managed by continuing enrollment and determining the sub classes later on a larger collection of enrolled candidates.

---

24 Rubin DB. For objective causal inference, design trumps analysis. The Annals of Applied Statistics. 2008;2(3):808-840.

25 Yue LQ. Statistical and regulatory issues with the application of propensity score analysis to nonrandomized medical device clinical studies. J Biopharm Stat. 2007;17(1):1-13; discussion 15-17, 19-21, 23-17 passim.

7.17.2. Variables to be Included in PS Model

The following tables list information to be used to construct variable for the PS modeling. Variables include demographic factors, baseline disease severity factors, radiographic factors, and site and surgeon factors. The final formulation of variables derived from the following factors will be defined by the statistician responsible for conducting the PS modeling and without regard to outcome data.

Variable	Location of Variable in CRF
Age	CRF Form 1
Gender	CRF Form 2
Race	CRF Form 2
Ethnicity	CRF Form 2
BMI	CRF Form 2
Duration of symptoms	CRF Form 2
Pain management	CRF Form 2
Prior treatment	CRF Form 2
Current or former smoker	CRF Form 2
Work Status	CRF Form 2
Cross-sectional area of spinal canal	Core Lab
Foraminal area	Core Lab
Diagnoses	CRF Form 4
Ortho/neuro surgeon	CRF Form 4
VAS-leg (max)	CRF Form 7
VAS-back	CRF Form 7
ODI	CRF Form 8
ZCQ physical function	CRF Form 9

7.18. Analysis of Safety

7.18.1. Adverse Events

Assessment of the safety of the coflex implant will be based on the incidence and seriousness of adverse events associated with the treatment.

Adverse event rates will be summarized by type of AE and for specific AEs in two ways: 1) per patient using counts and percentages and 2) by event, summarizing event counts by visit interval over time. Device and procedure related events will be summarized by seriousness. Events listings will be provided that include details such as relatedness, severity, onset and resolution status will be provide for all events and for relevant subsets of events such as serious events and related events.

All adverse events (AE) will be listed according to ICH guidelines. Additional tables presenting a survey of the incidence rates by treatment groups will be drawn up for the following classifications and items:

- Premature Termination, Serious Adverse Events and Causal Relationship
- Separate Presentation of Serious Adverse Events

7.19. Clinical Events Committee (CEC)

Adverse events will be evaluated by an independent Clinical Events Committee (CEC). The goal of this CEC process is to allow for uniform resolution of these types of study-related events and evaluations, and thus to eliminate any site-by-site variations in reporting. The CEC will review individual adverse event reports for the potential to reclassify the investigator's categorization of the events.

7.20. Software for Data Analyses

Validated clinical data will be provided by the data management CRO to the statistical CRO. Further data processing, constructing of indices, evaluation of theoretical and expected due status, statistical screening, etc. will be conducted using SAS version 9.4 or higher. Statistical procedures, which are not implemented in the standard SAS modules BASE, STAT and GRAPH, will be implemented using the SAS language or R version 3.2 or higher.

7.21. Reporting Procedures for Deviation from the Statistical Analysis Plan

Deviations from the Statistical Analysis Plan will be documented in the final report.

8. Data Management

8.1. Description of Procedures

All data in this study will be entered in to an Electronic Data Collection System managed by the CRO for this study. Once data on the eCRFs are considered complete (no missing fields) and accurate via monitoring and queries (see Study Management), and have been reviewed by the investigator, data will be reviewed by a data management contractor. The unique study database will be maintained and updated throughout the course of the study following predefined methodologies. A final copy of the database will be appropriately stored by the database contractor and/or Vertos Medical. This official database will serve as a reference for all data inquiries.

8.2. Data Cleaning

In the scope of the data management the data will be checked for completeness and plausibility. Open questions and missing values will be clarified using Data Correction Forms. Furthermore electronic cleaning procedures will be applied to further identify and resolve data inconsistencies. The data manager will check all discrepancies and will initiate the printout of the corresponding DCFs (queries). These forms have to be answered and signed by the Investigator.

After the data cleaning has been finished, the data will be regarded as "clean" if they show no conspicuous features with respect to criteria coordinated with the Sponsor or if all still remaining conspicuous facts can be explained.

9. Ethical and Legal Aspects

9.1. Institutional Review Board (IRB)

This trial can only be undertaken after full approval has been obtained through the IRB. The approval(s) have to cover the protocol and addenda, if applicable, as well as the current Patient

Information and Informed Consent Form as well as the product brochure and manufacturer information (if applicable).

During the trial the following documents will be sent to the IEC/IRB for their review:

- Changes to the product brochure and manufacturer information
- Reports of all Adverse Events that are rated serious, unexpected and associated with the investigational device.
- All protocol amendments and revised Patient Information and Informed Consent Form (if any).

For protocol amendments, which increase subject risk, the amendment and applicable Patient Information and Informed Consent Form revisions must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s).

Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the Investigator at intervals stipulated in their guidelines.

At the end of the trial, the Investigator will notify the IEC/IRB about the trial completion.

9.2. Good Clinical Practice

This trial will be conducted in accordance with the current ICH-GCP-guidelines as specified for medical devices in ISO 14155.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

9.3. Informed Consent Form

Prior to entry in the trial, the investigator must explain to potential subjects or their legal representatives the trial and the implications of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not impact on the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that competent authorities may access their records and authorized Sponsor's persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF) the subject or legally acceptable representative is authorizing such access.

The subject or legally acceptable representative will be given sufficient time to read the informed consent form and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the Informed Consent must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the written informed consent.

Subjects who are unable to comprehend the information provided can only be enrolled after obtaining written consent of a legally acceptable representative.

9.4. Liability and Insurance

The sponsor has product liability coverage. Because the coflex device is a commercially available implant, this liability coverage is sufficient.

9.5. Acknowledgement/Approval of the Clinical Investigation Plan

The coflex device is already PMA approved. Due to the additional investigations for patients, this trial has to be submitted to the FDA for approval.

9.6. Financial Disclosure

All the involved persons (main Investigators, co-Investigators, and study staff involved) have to sign the Investigator Financial Disclosure Questionnaire and declare that they work strictly according these declarations.

9.7. Confidentiality

All the involved main investigators have to confirm that they handle the information which is available in the handed over documents (Clinical Investigational Plan, etc.) strictly in confidence.

10. Administrative Procedures

10.1. Responsibility of the Sponsor

The Sponsor will ensure that the Investigator is:

- An appropriately qualified practitioner legally entitled to practice.
- Trained and experienced in the field of application of the device under consideration.
- Familiar with the background to - and the requirements of - the clinical investigation.

The Sponsor:

- Is in charge of the organization and the financing of the clinical trial. The mandate of any CRO within the trial organization is clearly defined by a separate contract. The overall responsibility for the trial remains with the Sponsor.
- Is responsible to contract a product liability insurance accordance with the legal requirements.
- Has to safeguard that the trial is not started before an approval of the responsible ethical committees are available.
- Will safeguard that appropriate information and/or training is given to the clinical Investigators in the use of the device in accordance with the Clinical Investigation Plan.
- Will judge (together with the Investigator) all Serious Adverse Events without delay and take all necessary steps to protect the subjects taking part in the clinical investigation.
- Is responsible that the regulatory authorities will be notified of incidents in accordance with the legal requirements (MDRs).

- Is in charge of a continuously evaluation and documentation of all SAEs and other safety relevant information. If necessary, interventions for the safety of the study patients have to be arranged.
- Is responsible for the quality of the devices tested. This covers production, packaging, labeling, testing, release and documentation of all investigated devices.
- Reserves the right to demand the exclusion of a patient from the clinical investigation in the case of severe protocol deviations or violations.
- Authorizes CRO to exclude Investigators from the clinical investigation because of severe protocol violations or because of fraud and misconduct.
- Is also entitled to terminate the clinical investigation prematurely due to continued protocol violations or because of technical or other shortcomings. If this should become necessary the Sponsor and the Investigator will wind up the proceedings after consideration and consultation, taking into account the protection of the patients' interests.
- Will arrange that remuneration agreements between Sponsor and Investigators will be laid down in separate contracts.

10.2. Responsibility and Qualification of the Investigator

The Investigator has to make themselves thoroughly familiar with the properties of the investigational device, which is described in the product brochure and manufacturer information.

The investigators ensures that there is sufficient time to carry out the clinical investigation, that adequate staffing and facilities are available for the complete duration of the clinical investigation, and that the planned number of patients can be recruited within the proposed period of time.

The investigator submits the Sponsor a current curriculum vitae for documentation purposes or submission to an IRB.

The investigator confirms in writing that he has read and understood the protocol, that he will work in compliance with the protocol, Good Clinical Practice and the regulatory requirements, that he will accept the function of the CRA and the inspections, that he is independent of the Sponsor, and that he will come to an agreement with the Sponsor about publication.

Together with the administration (in case the study site is based in a hospital) the investigator signs a contract with the Sponsor, which specified the duties and rights and his remuneration. Also, a signed a financial disclosure questionnaire is required.

The investigator fully informs all the staff who is involved in carrying out the clinical investigation or looking after the patients about all relevant aspects of the trial. It must be documented in writing if clinical investigation tasks are delegated.

The investigator will explain all aspects of the clinical investigation to the patient in a comprehensible manner, as mentioned in the written Patient Information, and will inform the patient as soon as possible of any new particulars that could influence the patient's willingness to participate in the clinical investigation. The Investigator has to confirm that he has informed the patient in this way with his signature on the Informed Consent Form.

The investigator will give the patient ample opportunity to ask questions, and will allow the patient sufficient time to reach a decision regarding participation. The Investigator will give the participant the written Patient Information and a copy of the signed and dated written Informed Consent Form.

He collects all data correctly and completely, records them in an appropriate source document transfers the necessary data to the eCRFs and signs the eCRFs.

The investigator informs the Sponsor and the CRO promptly if a Serious Adverse Event occurs.

Before trial start the Investigator will define all source documents that are used in this trial.

The investigator must keep a confidential patient list showing the patient's name and date of birth and the patient's number, so that an unambiguous identification of each individual patient is possible.

The trial participation of any study patient will be mentioned in the corresponding medical files for documentation and information of other physicians who are not involved in the trial but may take care of the patient.

The Investigator is responsible for ensuring that every patient can be identified by means of the patient list for 15 years after completion or termination of the clinical investigation. The patient list and other source data must be kept for at least 15 years.

10.3. Responsibility and Qualification of the CRO

The CRO will handle study preparation, coordination, monitoring, data management and evaluation according to the contract with the Sponsor.

10.3.1. Assessment of Clinical Study Sites

Additional data on each of the clinical study sites will be collected to assess the representativeness and generalizability of the study results. This data includes the size of the participating clinical center (number of beds), whether or not the hospital is a teaching hospital, and the geographic location of the institution (e.g. urban, suburban, or rural).

10.3.2. Notification of the Clinical Study

Following the protocol approval in the United States, the investigation will be listed on clinicaltrials.gov.

10.3.3. Study Management and Monitoring

An experienced CRA(s) will be available to advise the Investigator during the clinical investigation and to perform on site monitoring.

The CRA shall check and confirm that:

- The clinical Investigator(s) is (are) informed of the investigational status of the device and the requirements necessary to verify the performance of the device;
- The compliance with the Clinical Investigation Plan is maintained by periodic communications;
- Any deviation from the protocol is discussed with the clinical Investigator(s) and reported to and agreed with the Sponsor;
- Sufficient suitable staff and facilities are available at any trial site at any time to conduct the clinical investigation effectively and guarantee the safety of the study patients;
- All essential documents and contracts are signed by the appropriate persons;
- Any Investigator meets the patient recruitment targets or not;
- SAEs are recorded and reported to the Sponsor;

- The device is being used according to the documented instructions, and if modifications appear to be needed, either to the device or to the Clinical Investigation Plan, this is reported to the Sponsor;
- The trial documentation file is updated;
- A correctly filled in Informed Consent has been obtained of each patient before any trial related action has been performed;
- Withdrawal and/or non-compliance by the subject is being documented;
- The data in the electronic data capture system conforms with that in the source documents;
- Any reason for the termination of the clinical investigation has been documented.

The CRA must handle the patients' personal medical data confidentially, to which he/she has access to during inspection of inspecting the medical records and other source data. The relevant monitoring guidelines must to be followed.

10.3.4. Pre-Study Visit

During the Pre Study Visit Project Manager or Medical Director will verify the qualification of all involved persons whether according to their ability to conduct this trial.

Therefore the following points need to be verified:

- Does the Investigator have the possibility to recruit the amount of requested subjects according to the protocol?
- Are the trial-involved persons trained enough to cope with the investigational device according to the manufactures guidelines?
- Are the trial-involved persons trained enough concerning the content of the protocol?
- Has the main-Investigator sufficient experience in conducting an international clinical trial?
- Are the trial-involved persons willing to work in compliance with the Clinical Investigation Plan?

10.3.5. Study Initiation Visit

During the Study Initiation Visit it is the responsibility of the CRA to secure that the following documents are present in the trial documentation file:

- Written FDA approval,
- Written IRB approval,
- Members of the IRB and qualifications,
- Fully Executed NDA (Non-Disclosure Agreement),
- Signed clinical trial agreement,
- Signed financial agreement(s),
- Signed Clinical Investigation Plan,
- Signed Amendment(s), if applicable,
- Confidentiality Agreement(s), if applicable,
- "Statement of Investigator" (FDA/Sponsor), if applicable,
- Financial Disclosure Questionnaire,
- Delegation of Authority Log,
- Curricula vitae of the main Investigator, co-Investigator and study staff,
- Written Informed Consent Form,
- Site Training Log (core lab, database, reimbursement, etc.)

A Study Initiation Visit Report will be provided to the Investigator as a follow up to the Trial Initiation meeting.

During the initiation visit it must be ensured that the main-Investigator, co-Investigator and all study staff are sufficiently trained in correct conducting the trial in accordance to the Clinical Investigation Plan GCPs. Furthermore, the trial documentation file (Investigator file) and the source document worksheets and eCRF should be reviewed with the site.

10.3.6. Routine Monitoring Visits

The Clinical Research Associate (CRA) will perform all Monitoring Visits. To this purpose he/she has to check the points mentioned under “Study Management and Monitoring” and prepare a formal Monitoring Visit Report.

The monitoring frequency will be one visit every 8 weeks or as needed. The frequency of monitoring will depend on the recruitment status of each center. In order to avoid monitoring backlog the frequency might be increased.

10.3.7. Study Termination Visit

During the study termination visit all monitoring activities in the study center have to be finalized. The study file of the Investigator has to be checked and prepared for archiving, final questions have to be solved, study related devices and materials have to be collected, and final study-related documents have to be obtained. Therefore, the CRA will perform the following main activities:

- Resolve all outstanding issues,
- Verify that the Subject Identification Register is complete and filed in the Investigator file (Investigator file),
- Verify that all Informed Consent Forms and the updated subject log are completed and filed in the Investigator file.
- Ensure that any follow-up information on Adverse Events is obtained and has been recorded appropriately,
- Ensure that any documents maintained separately from the Investigator file during the trial are filed in the Investigator file
- Review the Investigator file and ensure that it is complete, amend if necessary,
- Ensure that all forms are completed correctly and collect copies according to the filing instructions,
- Ensure that all remaining eCRFs and other data collection tools are completed and collected,
- Verify that all Investigator copies of completed source document worksheets and other data collection tools are together and prepared for storage,
- Obtain completed Investigator Financial Disclosure Forms from the Investigator and the co-Investigator(s),
- Prepare and sign-off the Site Closure Report.

11. Trial Closure Considerations

The decision to close an investigational site upon trial completion will be made by the Project Manager or the Sponsor after intense discussion with the CRA. The Investigator must be informed by the CRA or the Project Manager about the considerations made to close his site. He has to be given the opportunity to comment on the arguments presented by the Sponsor in order to avoid the closure of the site.

If the Sponsor still wants to close the site, the site closure visit should be scheduled soon after completion of source document verification of the last case report form (CRF) and after the last queries have been solved. The Investigator should be present. The site should not be closed before the data cleaning process has been finalized and no further queries are expected.

An investigational site is considered ´closed´ when all required documents and trial supplies have been collected and a site close out visit has been performed. Site closure may also be initiated at any time by the Investigator, the IEC/IRB responsible for the investigational site, or the regulatory authorities.

The Sponsor reserves the right to close the investigational site or terminate the trial at any time if certain circumstances apply. Reasons for the closure of an investigational site or termination of a trial by the Sponsor may include:

- Successful completion of the trial at the center;
- The required number of subjects for the trial or multicenter-wide have been recruited;
- Failure of the Investigator to comply with the protocol or GCP guidelines;
- Safety concerns;
- Sufficient data suggesting lack of performance;
- Inadequate recruitment of subjects by the Investigator.

The reasons for premature site closure must be documented in writing.

12. Documentation and Use of Study Findings

All study related findings will be reported in comprehensive integrated study report in accordance with the ICH-Guidelines. This includes any deviations from the planned procedures if not already mentioned in an amendment to this CIP.

12.1. Use of Study Findings: Reports and Publications

The study results are used for marketing reasons and for the generation of medical knowledge. The Sponsor reserves the right to use the study findings for international registration purposes.

Data generated from the conduct of this study will be used to support Post-Approval requirements mandated by FDA.

Publication of the results of the study will follow Paradigm Spine Publication and Presentation Policy.

Directly after the last patient has completed the clinical investigation data cleaning will be finalized, the data base lock will be performed and arrangements will be made to prepare a final report (including a statistical report) which complies with the requirements GCP.

The Sponsor and the Principal Investigator as well as all other Investigators must approve the receipt of the final report by signature. The Investigator is under obligation to handle all clinical investigation data confidentially. Publication of clinical investigation data can take place by mutual agreement of Sponsor and Investigator.

The publication of data from medical investigations in reputable scientific journals and presentation of data at congresses and conferences is basically approved. Before publication, the

Sponsor has to be given sufficient time to check the manuscript (as laid down in the financial contract with the Investigator).

Legitimate interests of the Sponsor will be taken into consideration, like, for example, getting optimal patent protection/coverage, coordinating submissions to the health authorities, coordinating the clinical investigation with other investigations taking place in the same area, or protection of confidential data and information.

Planned publications have to be presented to the Sponsor. Legitimate objections can be raised within 6 weeks and should be taken into consideration by the Investigator.

Before any publication a mutual consent between Sponsor and Investigator should be obtained.

The study will be registered on Clinicaltrials.gov in compliance with 42 CFR Part 11. Results of the study, including an unanticipated early termination of the trial, will be posted to the Clinicaltrials.gov database at the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis.

13. DATA QUALITY ASSURANCE (AUDITING)

Throughout every part of the clinical investigation the quality management system of CRO will apply. The protocol, CRFs, monitoring, data input, evaluation and the clinical investigation report will be audited by CRO as laid down in the contract/accepted cost estimate between the CRO and the sponsor. The SOPs of CRO are taking into consideration, if not agreed otherwise. On site audits are not planned.

14. REFERENCES/LITERATURE

1 Caputy AJ, Luessenhop AJ., Long-term evaluation of decompressive surgery for degenerative lumbar stenosis, J Neurosurg. 1992 Jun;78(6):1010-1.

2 Kaech DL et al., The interspinous “U”: new restabilization device for the lumbar spine, Spinal Restabilization Procedures, Chapter 30, 355 – 362, 2002, Elsevier Science

3 Airaksinen O et al, Surgical outcome of 438 patients treated surgically for lumbar spinal stenosis, Spine 22(19) 1997, pp2278 – 2282

4 Iguchi T et al., Minimum 10-Year Outcome of Decompressive Laminectomy for Degenerative Lumbar Spinal Stenosis, SPINE Volume 25, Number 14, pp 1754–1759

5 Samani J, Study of a semi rigid interspinous “U” fixation system, 106 patients over six years, Spinal surgery, Child Orthopaedics, 1707, 2000

6 Stucki G et al., Measurement Properties of a Self-Administered Outcome Measure in Lumbar Spinal Stenosis. Spine. Vol. 21(7). pp. 796-803.

7 Pratt RK et al., The Reliability of the Shuttle Walking Test, the Swiss Spinal Stenosis Questionnaire, the Oxford Spinal Stenosis Score and the Oswestry Disability Index in the Assessment of Patients with Lumbar Spinal Stenosis. Spine Vol. 27 (1) pp. 84-91.

8 Mannion AF, et al., Development of a German version of the Oswestry Disability Index. Part 1: cross-cultural adaptation, reliability, and validity, Eur Spine J (2006) 15: 55–65; DOI 10.1007/s00586-004-0815-0

9 Mannion AF, et al., Development of a German version of the Oswestry Disability Index. Part 2: cross-cultural adaptation, reliability, and validity, Eur Spine J (2006) 15: 66–73; DOI 10.1007/s00586-004-0816-z

10 Katz JN et al., Seven- to 10-year Outcome of Decompressive Surgery for Degenerative Lumbar Spinal Stenosis, Spine: Volume 21(1) 1 January 1996 pp 92-97

11 Grogan J, Lumbar facet joint tropism does not accelerate degeneration of the facet joints, Am. J. Neuroradiol 18: 1325-1329, August 1997

12 Deen H. et al., Measurement of exercise tolerance on the treadmill in patients with symptomatic lumbar spinal stenosis: a useful indicator of functional status and surgical outcome, J. Neurosurg 83:27-30, 1995

13 Deen H. et al., Use of the Exercise Treadmill to Measure Baseline Functional Status and Surgical Outcome in Patients With Severe Lumbar Spinal Stenosis, Spine: Volume 23(2) 15 pp 244-248, 1998

14 Fairbank J.C.T., The Oswestry Disability Index, Spine Volume 25, Number 22, pp 2940–2953, 2000

15. APPENDICES

Appendix I	Case Report Forms
Appendix II	Instructions for use
Appendix III	Example text of Informed Consent Forms
Appendix IV	Patient Labeling
Appendix V	Radiographic Protocol
Appendix VI	Exponent Explant Protocol