CARBOCLEAR PEDICLE

SCREW SYSTEM

CLINICAL STUDY PROTOCOL

May 2017

CONFIDENTIAL

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Confidentiality Statement

This Investigational Protocol contains confidential information for the sole information and use of the principal investigator and its designated representatives participating in this clinical investigation, and the IRB/EC. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

1. GENERAL

1.1. STUDY SPONSOR

The proposed study for the CarboClear Pedicle Screw System will be sponsored by:

Sponsor Name: **CarboFix Orthopedics, Inc.**

Address: 7183 Beach Drive SW, Ste 1, Ocean Isle Beach, NC 28469, USA

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E-Mail: hila@carbo-fix.com

1.2. INVESTIGATIONAL DEVICE MANUFACTURER

Sponsor Name: CarboFix Orthopedics Ltd.

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Tel: Tel: +972-9-9511511

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E-Mail: hila@carbo-fix.com

1.3. INVESTIGATOR AND INVESTIGATION SITE

Investigator Name:

Investigator Position:

Investigation Site:

Address:

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E-Mail:

1.4. STUDY MONITOR

Monitoring of the study at US sites will be performed by the following Clinical Research Associate (CRA):

CRA Name: Colleen Smith CCS Research, Inc.
CCS Research, Inc., Massachusetts, USA
E-Mail: Colleen@carbo-fix.com

1.5. PROTOCOL SIGNATURES

Sponsor Representative:

Name	Title	Signature	Date

Investigator:

I have read this Protocol and agree to adhere to the requirements. I will provide copies of this Protocol and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the investigational product and the conduct of the study.

Name	Title	Signature	Date

2. CLINICAL STUDY SYNOPSIS

Device Name: CarboClear Pedicle Screw System ("CarboClear System").

Regulatory Status: Investigational Device; Exclusively for use in clinical investigations.

Study Design: A prospective, multi-center, confirmatory, single arm, study.
Results of the study will be compared to data from the literature.

Purpose: To demonstrate the safety and effectiveness of the CarboClear System, for skeletally mature DDD patients undergoing one level spinal fusion in combination with interbody fusion device, and requiring immediate, rigid, posterior spinal stabilization of the lumbar and/or sacral spine.

Intended Use: The CarboClear Pedicle Screw System is intended to provide rigid immobilization and stabilization of lumbar and/or sacral segments as an adjunct to fusion in patients with degenerative disc disease (DDD) at one level from L2 to S1, with up to Grade I spondylolisthesis. DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies. Patients should be skeletally mature and have at least six months of non-operative treatment.
The CarboClear Pedicle Screw System is designed for use with intervertebral body fusion device and with autogenous and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft.

Procedure: Implantation of the investigational device and an FDA cleared PEEK interbody fusion device (either Medtronic's Capstone PEEK Spinal System, or Medtronic's Crescent PEEK Spinal System), using PLIF or TLIF. Posterolateral spinal fusion may also be performed, according to the physician discretion, using autogenic bone graft (from local and/or iliac crest bone) and/or allogenic bone graft.

Number of Subjects: A total of 55 subjects will participate in the study, with up to 15 patients recruited in this site. At least 30 patients will be enrolled in US sites.

Study Duration: The study is expected to last up to 36 months (total duration), including patient enrollment and a post-operative follow-up period of 24 months per subject.

Primary Outcome Measures:

- **Fusion**: evaluated radiographically (by AP, lateral and flexion/extension X-Rays) at 24 months; fusion is defined as:
  a. Angular motion < 3º; AND
  b. Translational motion < 3 mm; AND
  c. Presence of continuous bridging bone between the involved motion segment, *i.e.*:
     - Presence of interbody (between endplates) bridging bone and absence of radiolucency > 50%; OR
     - Presence of left posterolateral bridging bone; OR
     - Presence of left posterolateral bridging bone.
- **Pain (low back and/or leg/s)**: assessed based on Visual Analogue Scale (VAS), at 24 months; defined as an improvement of at least 20 mm on a 100 mm VAS from the baseline level.
- **Function**: assessed by Oswestry Disability Index (ODI), at 24 months; defined as an improvement of at least 15 points from the baseline level.
- **Safety**:
  - No worsening in neurological status (motor, sensory, reflex, straight leg raising, and tenderness assessments) and no new permanent neurological deficits present for at least 2 successive visits at or beyond 6 months (out to 24 months);
  - Absence of device-related serious adverse events through 24 months;
  - Absence of subsequent surgical interventions at the index level through 24 months.

Secondary Outcome Measures:

- **Subject's Overall Well-Being**: assessed by 12-Item Short Form Health Survey (SF-12), at 24 months;
- **Satisfaction**: assessed based on VAS, at 24 months;
- **Donor Site Pain**: assessed based on VAS, at 24 months;
- **Operation time**;
- **Blood loss**.

Follow-Up:

Radiographic (AP, lateral and flexion/extension X-Rays) and clinical evaluations.
Follow-up sessions at 6 weeks, 3 months, 6 months, 12 months, and 24 months postoperatively, and then annually, until the last patient has completed 2-year follow-up..

Inclusion Criteria:

1. Subject has degenerative disc disease (DDD) at one level, from L2 to S1 vertebrae, with up to Grade I spondylolisthesis.
   DDD is defined as back pain and/or radicular leg pain with degeneration of the disc confirmed by patient history, radiographic studies, and physical examination, with one or more of the following factors (as measured radiographically, either by CT, MRI or plain film, myelography, discography, *etc*.):
   - osteophyte formation of facet joints or vertebral endplates;
   - decreased disc height, on average by > 2 mm;
   - scarring/thickening of ligamentum flavum, annulus fibrosis, or facet joint capsule;
   - herniated nucleus pulposus;
   - facet joint degeneration/changes;
   - vacuum phenomenon.
2. Subject is candidate for single level intervertebral fusion, with or without posterolateral fusion, with implantation of intervertebral body fusion device and supplemental fixation.
3. Subject age is between 21 – 72 years, and subject is skeletally mature.
4. Pre-operative low back and/or leg/s pain (debilitating pain that causes a significant disturbance of the routine daily physical activities) ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS).
5. Pre-operative Oswestry Disability Index (ODI) score ≥ 40

percentage-point, indicating at least moderate disability (interpreted as moderate/severe disability).

6. Low back and/or leg/s pain is unresponsive to prior non-surgical management for a minimum of six months. Non-operative treatment includes pain medication, physical therapy and/or injections.
7. Patient must understand and sign the informed consent.
8. Patient is willing and able to meet the proposed follow-up schedule including return to follow-up visits and complete necessary study paperwork.
9. Patient is willing and able to follow the postoperative management program.

Exclusion Criteria:

1. Previous fusion or fusion attempts, including anterior fusion or posterolateral fusion, at the index level.
2. Previous fusion or fusion attempts at the adjacent levels.
3. Prior decompression procedures that include removal of soft and bone tissue at the index or adjacent levels.
4. Patient is not skeletally mature.
5. Degenerative spondylolisthesis greater than Grade I.
6. Spinal instability at the index level with ≥ 3 mm translation and/or ≥ 5 degrees angulation. Determination of instability will be assessed using flexion/extension lateral view radiographs.
7. Isthmic spondylolisthesis.
8. Radiographically confirmed moderate or severe spinal stenosis with associated neurogenic claudication.
   Definitions:
   - Radiographically confirmed moderate/severe stenosis is defined as reduction of >50% of central and/or foraminal canal diameter compared to the adjacent uninvolved levels.
   - Neurogenic claudication is leg, groin, or buttock pain and/or numbness that worsens with walking or erect posture and is relieved with flexion of the spine.
9. Systemic infection or infection at the site of surgery.
10. Metabolic bone disease, such as osteopenia, osteoporosis, and osteomalacia. A screening Questionnaire for osteoporosis,

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 measured T-score less than or equal to -2.5 (WHO definition).

11. History of Paget's disease or other bone pathologies, whether acquired or congenital, including renal osteodystrophy, untreated or uncontrolled hyperthyroidism, hypothyroidism, or hyperparathyroidism, Ehrlers-Danlos-syndrome, osteogenesis imperfecta, achondroplasia, tuberculosis.
12. Personal and/or familial history NF2, and/or spinal tumor.
13. Ankylosing spondylitis.
14. Diffuse idiopathic skeletal hyperostosis (DISH) syndrome.
15. Active hepatitis (viral or serum) or HIV positive, renal failure, systemic lupus erythematosus, or any other significant medical conditions which would substantially increase the risk of surgery.
16. Immune deficiency disease.
17. Patient is receiving immunosuppressive or long-term steroid therapy.
18. Active malignancy or other significant medical comorbidities.
19. All concomitant diseases that can jeopardize the functioning and success of the patient.
20. Allergy to any component of the investigational device, including carbon fiber-reinforced polyetheretherketone (CFR-PEEK), titanium, and tantalum.
21. Pregnancy, or female subject interested in become pregnant during the duration of the study.
22. Current chemical dependency (*e.g.*, drug and/or alcohol abuse, according to DSM-V definition), as well as those with a history of such abuse.
23. Uncontrolled depression, psychosis, or other symptoms of a mental disorder that, in the investigator's opinion, likely would make the subject unable to comply with the study procedures and could affect the study outcome.
24. Treatment with drugs that may interfere with bone metabolism, such as glucocorticosteroids, calcitonin, bisphosphonates, bone

therapeutic doses of fluoride, bone therapeutic doses of vitamin D or vitamin D metabolites, and treatment by chemotherapy.

25. Morbid obesity (BMI ≥ 40).
26. Current smokers (including 3 months prior to surgery).
27. Scoliosis, Cobb angle greater than 11°.
28. Vertebral fractures.
29. Severe muscular, neural or vascular diseases that endanger the spinal column.
30. Missing bone structures, due to severely deformed anatomy or congenital anomalies, which make good anchorage of the implant impossible.
31. Paralysis.
32. Current use of other investigational drug or device.
33. The patient is involved in a worker's compensation case or spine-related litigation.
34. The patient is a prisoner.

3. INTRODUCTION

Chronic low back pain (CLBP) occurs in up to 60% - 80% of the adult population in the USA, with up to 5% experiencing this pain annually [1, 2, 3]. CLBP is a leading cause of morbidity and disability, thus constituting a leading health and economic challenge. It has been recognized that in some cases axial low back pain is secondary to dehydration and biochemical changes of the intervertebral disc. A degenerative cascade has been suggested by Kirkaldy-Willis [4], describing the pathophysiologic process as it affects the lumbar spine and individual motion segments. The term "degenerative disc disease" (DDD) has been coined for this entity. It should be noted, that degenerative changes may or may not be associated with clinical symptoms. Vast scientific reports have described degenerative imaging findings in asymptomatic population [5, 6]. The high prevalence of the degenerative process in both symptomatic and asymptomatic subjects limits the ability to correlate anatomic derangement and clinical symptoms [7]. Also, there is lack of consensus regarding the terminology and standardized clinical definition of DDD.

Most cases of low back pain are self-limiting in that only 7% of the patients have symptoms that persist beyond two weeks, with only 1% of those requiring prolonged treatment and even fewer eventually requiring surgical intervention [8]. The primary

[1] Guo HR, Tanaka S, Halperin WE, Cameron LL. Back pain prevalence in US industry and estimates of lost workdays. *Am J Public Health* 1999; 89(7):1029-1035.

[2] Mazroa AL, Mohammad A. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96.

[3] Andersson GB Epidemiological features of chronic low-back pain. Andersson GB. *Lancet* 1999 Aug 14;354(9178):581-585.

[4] Kirkaldy-Willis WH, Wedge JH, Yong-Hing KJR. Pathology and pathogenesis of lumbar spondylosis and stenosis. *Spine* 1978;3:319-28.

[5] Roh JS, Teng AL, Yoo JU, *et al.* Degenerative disorders of the lumbar and cervical spine. *Orthop Clin North Am* 2005;36:255–262.

[6] Dickerman RD, Zigler JE. Discogenic back pain. In: Spivak JM, Connolly PJ, eds. Orthopaedic Knowledge Update Spine 3. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2006:319–329.

[7] Modic MT, Ross JS. Lumbar degenerative disk disease. *Radiology* 2007; 245: 43-61.

[8] Report of the Quebec Task Force on Spinal Disorders. Scientific approach to the assessment and management of activity-related spinal disorders. A monograph for clinicians. *Spine* 1987 Sep;12

treatment for the majority of patients with DDD is non-operative. A wide variety of non-operative treatments are available including physical therapy (both active and passive modalities), medications (including analgesics, anti-inflammatories, muscle relaxants, and antidepressants), injections (both epidural and facet injections), patient education, chiropractic manipulation, traction, bracing, and acupuncture. However, if symptoms persist and/or progress despite non-operative management (particularly to the point of significantly impacting quality of life and the ability of the patient to function), surgery becomes an option. It has been recognized that surgery has favorable outcome for selected population that has failed non-operative treatment.

The current surgical standard of care for treating lumbar degenerative disease includes interbody fusion (ALIF, PLIF, TLIF), combined with posterolateral arthrodesis and pedicle screw systems fixation [9]. Over the last few decades, posterior pedicle screws instrumentation have evolved and revolutionized surgical care of various spinal disorders. Presently, pedicle screw systems are the workhorse of spinal instrumentation for the adult spine. Since their introduction in 1969, numerous advances in surgical and instrumentation techniques have been adopted, leading to continues progress in clinical outcomes [10].

The evolution of biomaterials assigned for these systems contributed to this progress. Titanium has gained wide popularity and has largely replaced conventional stainless steel. However, metallic implants possess several inherent shortcomings, including that metal alloys may severely degrade the quality of images of modern imaging techniques (CT and

(7Suppl):S1-59.

[9] Zigler JE, Delamarter RB. Does 360° lumbar spinal fusion improve long-term clinical outcomes after failure of conservative treatment in patients with functionally disabling single-level degenerative lumbar disc disease? Results of 5-year follow-up in 75 postoperative patients. *Int J Spine Surg*. 2013 Dec 1;7:e1-7.

[10] Gaines RW Jr. The use of pedicle-screw internal fixation for the operative treatment of spinal disorders. *J Bone Joint Surg Am*. 2000 Oct;82-A(10):1458-76.

MRI) due to metal-induced artifacts, and therefore may prevent accurate postoperative assessment of region of interest near the implants [11, 12, 13].

Carbon fiber-reinforced-polyetheretherketone composite (CFR-PEEK) has been suggested to overcome these limitations. The potential advantages of this composite material include inherent radiolucency and MRI and CT compatibility, resulting in negligible implant-induced artifacts, and superior fatigue life in compared to traditional implants. In addition, CFR-PEEK composites are biocompatible, and are rigid with structural stiffness equivalent to metallic biomaterials. All of those properties are ideal for spinal surgical implants. CFR-PEEK based spinal cages and other CFR-PEEK bone implants are cleared and in clinical use, and multiple studies reported their safety and effectiveness [14, 15].

The aim of the current study is to evaluate the safety and effectiveness of a novel CRF-PEEK pedicle screw system, the CarboClear Pedicle Screw System ("CarboClear System"). This is a rigid, pedicle screw system, intended to provide immediate immobilization and stabilization of the lumbar and/or sacral spine in DDD patients undergoing spinal fusion. The CarboClear System comprises polyaxial pedicle screws, longitudinal rods, and locking elements. The implants are made of CFR-PEEK with radiopaque markers. The threaded portion of the pedicle screws is encased within a thin titanium shell. The design and dimensions of the implant components are similar to those of other, market-available pedicle screw systems. The implantation technique and the instrumentation used during the operation are also similar to those used for other, cleared, pedicle screw systems.

[11] Rutherford EE, Tarplett LJ, Davies EM, Harley JM, King LJ, Lumbar spine fusion and stabilization: hardware, techniques, and imaging appearances**.** *Radiographics*, 2007;27(6):1737-1749.

[12] Romero-Muñoz LM, Alfonso M, Villas C, Zubieta JL, Effect of brightness in the evaluation of lumbar pedicular screws position: clinical study. *Musculoskeletal Surgery*, 2013;97(2): 159-164.

[13] Stradiotti P, Curti A, Castellazzi G, Zerbi A, Metal-related artifacts in instrumented spine. Techniques for reducing artifacts in CT and MRI: state of the art. *Eur Spine J*, 2009;18(1):102–108.

[14] Kurtz SM, Devine JN. PEEK biomaterials in trauma, orthopedic, and spinal implants. *Biomaterials* 2007 Nov;28(32):4845-69. Epub 2007 Aug 7.

[15] Vannabouathong C, Sprague S, Bhandari M, Li CS. The Use of Carbon-Fiber-Reinforced (CFR) PEEK Material in Orthopedic Implants: A Systematic Review. *Clin Med Insights Arthritis Musculoskelet Disord*. 2015 Feb 23;8:33-45.

Pre-clinical testing indicates that biomechanical performance of the system is similar to that of titanium pedicle screw systems. In addition, the system is being clinically investigated outside the USA, with good interim results.

This study is designed to demonstrate the safety and effectiveness of the CarboClear System for lumbar/sacral fusion requiring immediate, rigid stabilization of the spine.

4. DEVICE DESCRIPTION

4.1 DEVICE INTENDED USE/INDICATIONS FOR USE

The CarboClear Pedicle Screw System is intended to provide rigid immobilization and stabilization of lumbar and/or sacral segments as an adjunct to fusion in patients with degenerative disc disease (DDD) at one level from L2 to S1, with up to Grade I spondylolisthesis. DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies. Patients should be skeletally mature and have at least six months of non-operative treatment.

The CarboClear Pedicle Screw System is designed for use with intervertebral body fusion device and with autogenous and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft.

4.2 SYSTEM DESCRIPTION

The CarboClear Pedicle Screw System ("CarboClear System") is composed of implants in various dimensions, used to build a spinal construct; and of a set of surgical instruments, intended to assist in the insertion and placement of the implants. Each of these components is described below.

4.2.1 IMPLANT DESCRIPTION

CarboClear System comprises polyaxial pedicle screws, longitudinal rods, and locking elements.

The implants are made of carbon fiber-reinforced polyetheretherketone (CFR-PEEK) with radiopaque markers. The threaded portion of the pedicle screws is encased within a thin titanium shell.

4.2.1.1 Polyaxial Pedicle Screws

The polyaxial pedicle screws comprise a spherical head enclosed within a housing ("tulip"), enabling screw positing in a variety of angles and facilitating connection of the rod. Both cannulated and non-cannulated screws are available. The cannulated screws include a lumen of 1.3 mm diameter, to enable their insertion into the bone over a guide wire.

The screws are made of CFR-PEEK, and their threaded portion as well distal tip are encased within a 0.1 mm thickness shell, made of pure titanium (Grade I or II, per ASTM F 67), so that the screw portion that contacts the bone is made of titanium. The titanium shell is a sealed, non-porous, coating. It enables screw visualization under imaging, during screw introduction into the vertebra, as well as post-operatively. As the metal content in the screw is minimal, the metal-induced artifacts seen in CT/MRI imaging are minimal compared to all-metal pedicle screw systems.

The Pedicle Screw is depicted in **Figure 1**. Each pedicle screw is provided to the user as a "pedicle screw assembly", together with a tulip-like component that surrounds the screw spherical head (refer also to **Figure 2** below). The tulip, made of CFR-PEEK, includes a tantalum wire along its perimeter, to allow its visualization under imaging.

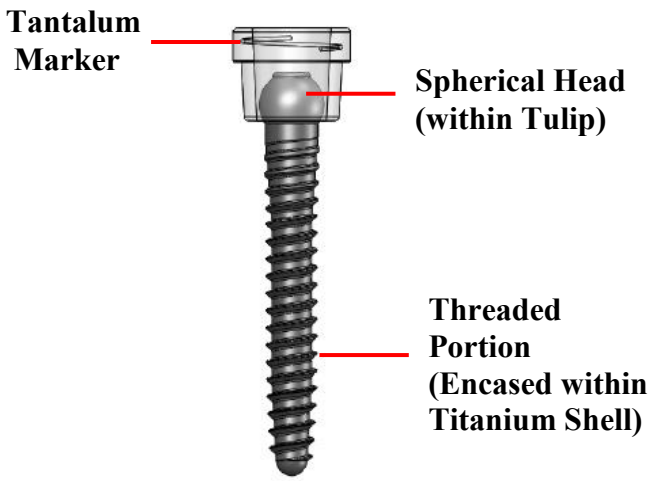


Figure 1: CarboClear System - Pedicle Screw

The pedicle screws are available in diameter of 5.5 mm, 6.5 mm and 7.5 mm, in lengths ranging from 35 mm to 55 mm (depending on screw diameter), in 5 mm increments.

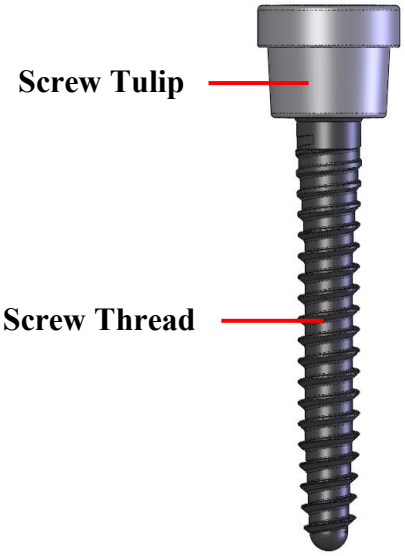


Figure 2: CarboClear System - Pedicle Screw Assembly

4.2.1.2 Rods

Longitudinal rods, of 6.0 mm diameter, available in lengths ranging from 30 mm to 220 mm. The rods are provided pre-cut, either straight or pre-contoured. The curved rods are provided with the following optional curvature radii: light curve - radius of 440 mm; moderate curve - radius of 240 mm; and prominent curve - radius of 120 mm).

A tantalum wire is incorporated along the long axis of the CRF-PEEK rods, thus enabling their visualization under imaging.

The curved and straight rods are depicted in **Figure 3**.

Figure 3: CarboClear System – Curved (Left) and Straight (Right) Rods

4.2.1.3 Locking Element

The component is made of CRF-PEEK and comprises a tantalum marker, to provide for its visualization under imaging.

At its upper portion, the locking element includes a lumen to accommodate the rod. During operation, the lower portion of the locking element is positioned within the cavity of the screw tulip, above the screw spherical head. In order to lock the implant components, the lower portion of the locking element is pressed against the tulip using dedicated instrumentation.

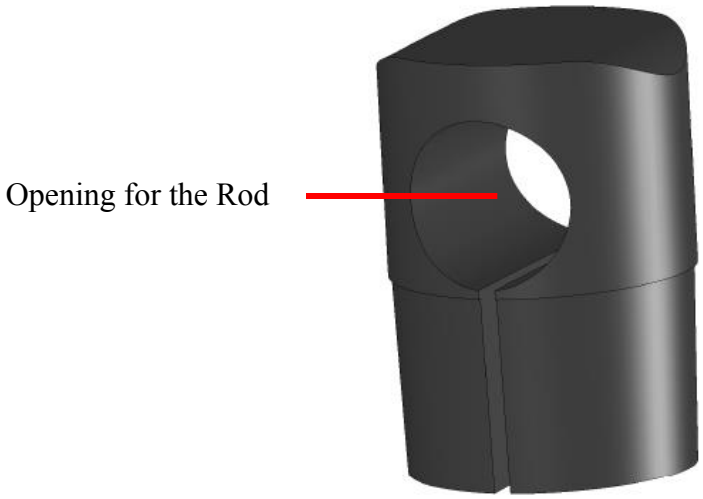


Figure 4: CarboClear System – Locking Element

Prior to final locking, the physician may slide the locking elements along the rod, to locate them at a desired position, and afterwards to lock them at that position. The locking elements may be provided already mounted over the rod, as depicted in **Figure 5**.

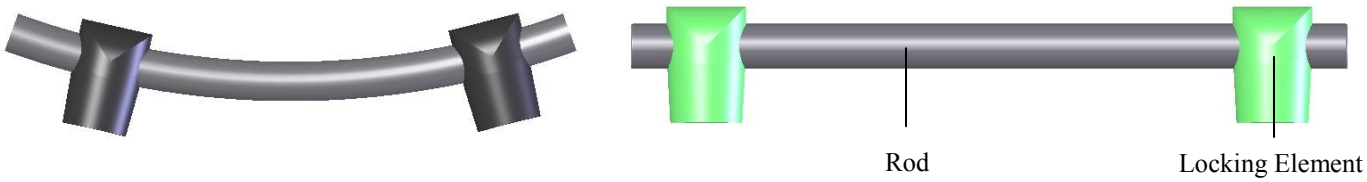


Figure 5: CarboClear System – Locking Elements Mounted on a Straight Rod (Right); and on a Curved Rod (Left)

4.2.1.4 Implant Assembly

Once assembled and locked, the CarboClear implant provides for a rigid construct, with no relative motion between its components. The construct (**Figure 6** (standalone) and **Figure 7** (attached to a spinal model)) provides for immediate stabilization and immobilization of the involved spinal segment.

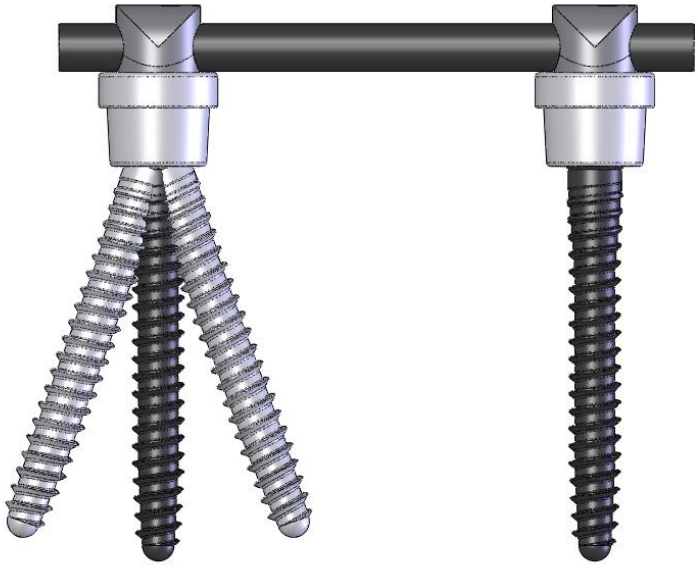


Figure 6: CarboClear System – Assembly of Implant Components

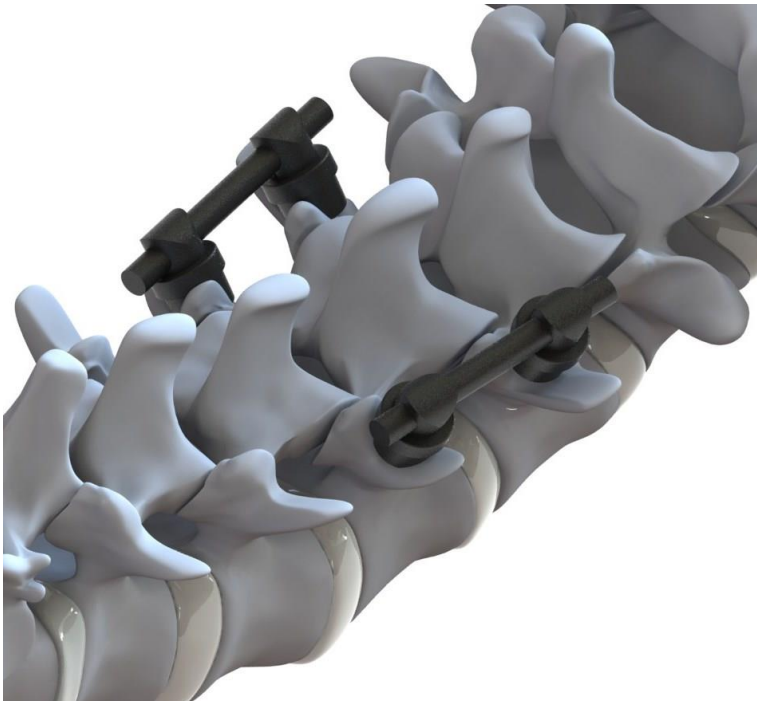


Figure 7: CarboClear System – Assembly of Implant Components, Attached to A Spinal Model

Table 1 summarizes the suggested implant components of the CarboClear System and their characteristics (materials and dimensions). Implant dimensions are within the range of dimensions seen in similar pedicle screw systems available on the market.

Table 1: CarboClear System – Implant Components

Implant Component	Material	Thread Diameter [mm]	Length [mm]	ROM [Degrees]
Polyaxial Pedicle Screw	CFR-PEEK; Screw shank - CP Ti shell; Tulip includes a Ta wire	5.5 *	35, 40, 45	40
		6.5 **	35, 40, 45, 50	30
		7.5 **	35, 40, 45, 50, 55	20
Rod ***Straight***	CFR-PEEK, with Ta wire	6.0	30 – 120 (5 mm steps)	-
Rod ***Curved (Moderate) / Curved (Prominent)***			30 – 80 (5 mm steps); 90 – 200 (10 mm steps)	-
Rod ***Curved (Light)***			30 - 220 (10 mm steps)	-
Locking Element	CFR-PEEK, with Ta marker	-	-	-

* Provided non-cannulated
** Provided either cannulated or non-cannulated

4.2.2 SURGICAL INSTRUMENTS

The instrumentation to be provided with CarboClear System is used for bone preparation and implant introduction and placement (as well as for implant removal, if required).
The instruments are, in general, multi-use surgical instruments, made of metal (such as stainless steel complying with ASTM F 899 or ASTM F 138) and polymeric material (*e.g.*, PEEK and propylux). They are similar to instruments used with other market-available pedicle screw systems, and to instruments supplied with other systems by the Company. Some accessories, such as guide wires, may be provided for single use.

The instrumentation for the CarboClear System includes the following components:

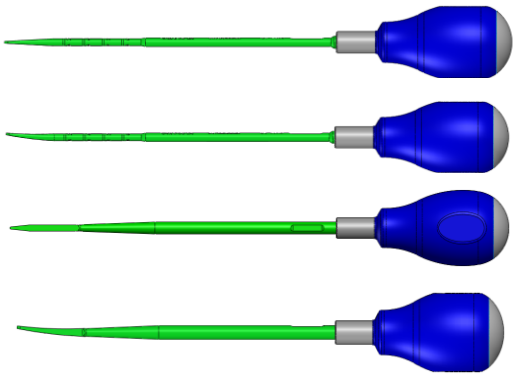
Pedicle Awl

Used to gain access through the bone cortex into the pedicle.

Pedicle Probes

Straight and curved, pointed or blunt, pedicle probes, intended to tunnel through the pedicle cancellous bone into the vertebral body.

The probes include depth markings, to facilitate the assessment of pedicle screw appropriate length.

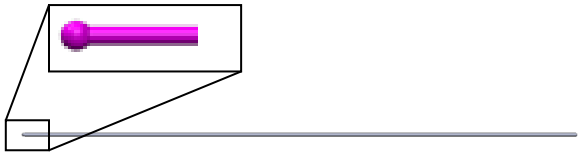


Pedicle Feeler

A ball-tipped device, used to verify pedicle wall integrity prior to tapping. It is marked to assist in the assessment of pedicle screw length.

1.5 mm Guide Wire

A ball-tipped guide wire. May be used to maintain trajectory during tapping and reaming.

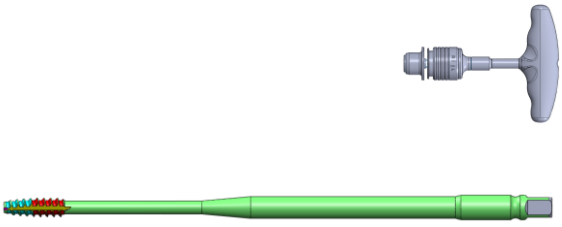


1.1 mm Guide Wire

May be used to maintain trajectory for the insertion of the cannulated pedicle screw.

Bone Taps

Cannulated taps, with diameter range of 4.5 - 7.5 mm. Used with a dedicated handle, to prepare the pedicle screw canal. May be used over the guide wire. The taps are marked to



assist in the assessment of pedicle screw length.

Pedicle Surface Reamer

May be used, if required, to ream the surface of the pedicle in order to allow accommodation of the pedicle screw head and tulip. The reamer is cannulated to enable reaming over the guide wire.

X-Ray Markers

May be used for radiographic verification of pathway positioning. Available in notched or smooth options, to distinguish right or left placement and to assess screw length.

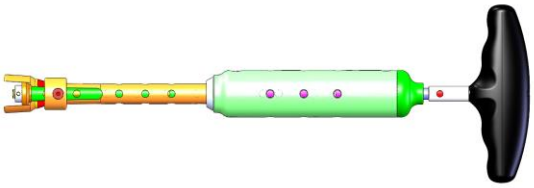
The markers are used with a dedicated inserter.

X-Ray Marker, Left

X-Ray Marker, Right

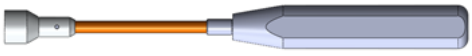
Pedicle Screw Screwdriver

A dedicated screwdriver, intended for the insertion of the pedicle screw into the pedicle. It is cannulated and may be used over the guide wire.



Tulip Adjusters

Used in case adjusting of the tulip orientation is required.



Rod Measuring Templates

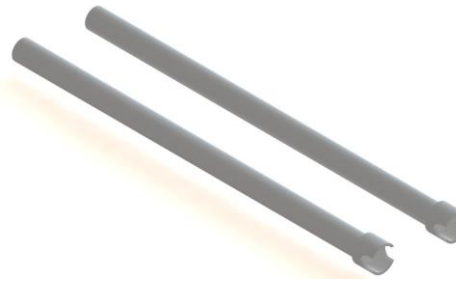
Straight and curved bendable rods, in several lengths, used to aid in selecting the proper rod. May be used with the Rod Holding Forceps.

Rod Holding Forceps (& X-Ray Marker Inserter)

May be used to securely hold the rod for its placement and positioning within the implant construct.

Rod & Locking Elements Holder

Used to securely hold the locking elements and the rod, for their placement and positioning within the implant construct.



Rod Pusher

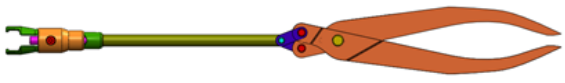
Used to push the rod for its location in place, if required.

Distractor

Used to perform distraction, in case required.

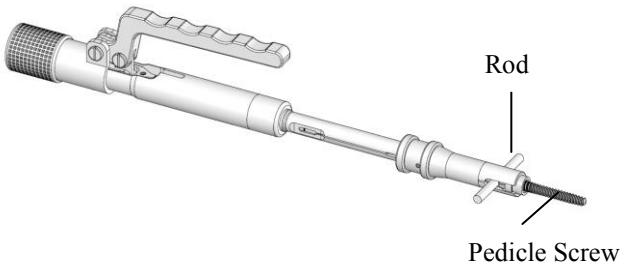
Persuader

The persuader may be used for partial locking.



Locking Device

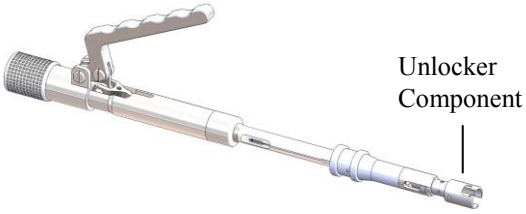
Used to press the locking element against the screw's tulip, in order to lock the screw-rod construct at a desired angle.



Disassembly Device

Used to open (disconnect) the locked rod-screw construct, in case re-positing or removal of the implant is required.

The unlocker component is connected to the distal end of the Locking Device.



Pedicle Screw Extractor (for damaged screw)

The screw extractor, assembled to the T-handle, may be used in case removal of a damaged (*e.g.*, broken) pedicle screw is required. The handle should be counter-clockwise rotated, to remove the pedicle screw. The extractor is available in three dimensions, to comply with the different diameters of the pedicle screw.

Additional surgical instruments, such as mallet may also be provided, to assist in the procedure, when required.

4.2.3 PRINCIPLES OF OPERATION

The implant components of the CarboClear System are implanted in a similar manner to that used for the implantation of other pedicle screws systems available on the market, as an adjunct to vertebrae fusion procedure.

A detailed operational procedure is described in the Surgical Technique (**Appendix A**).
In short, the implants of the CarboClear System are introduced in a standard approach. Following preparation of the vertebral pedicles, the screws are inserted into the vertebral body via the pedicles. A rod with two or more locking elements is then placed at each side over adjacent screws, to longitudinally connect them. The locking elements may slide along the rod, to be located at a desired position. Initial (partial) locking is conducted by pressing the locking element against the screw' tulip. At this stage, distraction may be performed, if required. Following confirmation of implant components position, a final, firm locking of the rod to the screws is performed using the locking device.

5. INVESTIGATIONAL PLAN

5.1 PURPOSE

The purpose of this clinical investigation is to demonstrate the safety and effectiveness of the CarboClear Pedicle Screw System ("CarboClear System"), for skeletally mature DDD patients undergoing one level spinal fusion, in combination with interbody fusion device, and requiring immediate, rigid, posterior spinal stabilization of the lumbar and/or sacral spine.

5.1.1 OUTCOME MEASURES

The following outcome measures will be evaluated in subjects participating in the study:

Primary Effectiveness and Safety Outcome Measures:

- **Fusion**: evaluated radiographically (by AP, lateral and flexion/extension X-Rays) at 24 months; fusion is defined as:
    a. Angular motion < 3º [16]; AND
    b. Translational motion < 3 mm; AND
    c. Presence of continuous bridging bone between the involved motion segment [17], *i.e.*:
        - Presence of interbody (between endplates) bridging bone and absence of radiolucency > 50%; OR
        - Presence of left posterolateral [18] bridging bone; OR
        - Presence of left posterolateral [18] bridging bone.

[16] In addition to angular motion of 3 degrees, the Company will provide fusion data and analysis using a threshold of 5° of angular motion. Additional information is provided in **Section 3.10.1**.

[17] The definition above calls for "continuous" bridging bone (with or without trabeculation). That is, solid bridging with no intervening fractures or discontinuities. Conventional plain film imaging rarely supports visualization of trabeculae.

[18] Right posterolateral - between the right facets, pedicle and/or transverse processes; left posterolateral - between the left facets, pedicle and/or transverse processes.

- **Pain (low back and/or leg/s)**: assessed based on Visual Analogue Scale (VAS), at 24 months; defined as an improvement of at least 20 mm on a 100 mm VAS from the baseline level.
- **Function**: assessed by Oswestry Disability Index (ODI), at 24 months; defined as an improvement of at least 15 points from the baseline level.
- **Safety**:
    - No worsening in neurological status (motor, sensory, reflex, straight leg raising, and tenderness assessments) and no new permanent neurological deficits present for at least 2 successive visits at or beyond 6 months (out to 24 months);
    - Absence of device-related serious adverse events through 24 months.
    - Absence of subsequent surgical interventions at the index level through 24 months.

Secondary Outcome Measures:

- **Subject's Overall Well-Being**: assessed by 12-Item Short Form Health Survey (SF-12), at 24 months;
- **Satisfaction**: assessed based on VAS, at 24 months;
- **Donor Site Pain**: assessed based on VAS, at 24 months;
- **Operation time**;
- **Blood loss**.

5.2 STUDY DESIGN

A prospective, multi-center, confirmatory, single arm, study.

A total of up to 55 subjects with DDD at one level from L2 to S1, who have failed to improve with conservative treatment for at least six months prior to enrollment, will participate in this study. At least 30 patients will be enrolled at US sites with the rest being enrolled in sites outside the US.

All patients will be implanted with the investigational device and an FDA cleared PEEK interbody fusion device (Medtronic's Capstone PEEK Spinal System (K073291, K103731, and more); or Medtronic's Crescent PEEK Spinal System (K094025, K133216, and more)), using PLIF or TLIF approach, and undergo interbody spinal fusion. According to the physician discretion, posterolateral spinal fusion may also be performed, using autogenic bone graft (from local and/or iliac crest bone) and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft. As Medtronic's Capstone and Crescent Systems are cleared only with autogenous bone graft, only autogenous bone graft will be packed into the cage. In case posterolateral fusion is also conducted, either autogenous bone graft or allogenic bone graft, as detailed above, may be used at this location.

Pre-clinical data (bench testing), as described in the Investigator Brochure, demonstrated equivalency to cleared, rigid, metal, pedicle screw systems with similar intended use, both in terms of test results values and tests failure modes. In addition, clinical data regarding the use of the subject device, which is currently available from an on-going, out-of-the-US (OUS), multi-center study, and is summarized in the Investigator Brochure, also supports the effective and safe use of the investigational device. The discussed confirmatory clinical study is designed to further support the safety and effectiveness of the CarboClear System.

The results of the suggested study will be evaluated in relation to historical-based data, derived from the literature and described in **Section 5.2.1**.

Comparison to retrospective data from the literature regarding metal pedicle screw systems used in conjunction with interbody fusion device will be made in terms of efficacy and safety.

Individual patient success (*i.e.*, overall success) is defined as a composite endpoint. A patient will be considered a "success" if all primary effectiveness and safety outcome measures listed above are met. As detailed later in this document, the statistical analyses of the suggested study will be descriptive in nature.

During the clinical investigation, the patients will be evaluated preoperatively (baseline), intraoperatively, at discharge, and postoperatively at 6 weeks, 3 months, 6 months, 12 months and 24 months, and then annually, until the last patient completed 2-year follow-up. Radiographic endpoints will be evaluated by two independent reviewers at an imaging core laboratory (Medical Metrics, Inc., Texas). In the case of a disagreement between the two radiographic assessors, a third independent reviewer will evaluate the radiographic images to adjudicate the findings. In addition, a CT scan will be acquired for subjects in which bridging bone status could not be determined form X-Rays, at each time point starting at 6 months post-operatively.

At each evaluation time point, as applicable, the primary and secondary endpoints shall be evaluated (*e.g.*, pain and function evaluations based on patient questionnaires shall be performed pre-operatively and starting at 6-week follow-up visit; fusion assessment will be made starting at 6-month). Complications and adverse events will be evaluated at each follow-up visits and over the course of the clinical trial. Detailed evaluation schedule is provided in **Table 8**.

5.2.1 LITERATURE CONTROL

In order to identify studies for the literature control, a poly-phasic approach was used:
First, Table 6 of the *FDA Executive Summary, Prepared for the May 22, 2013 Meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee, 2013 – Classification Discussion, Pedicle Screw Spinal Systems (Certain Uses – Class III Indications for Use*) ("FDA Executive Summary") was used for extracting articles believed to have valid scientific evidence.
The FDA Executive Summary was reviewed. This document includes a survey of literature aimed at establishing the safety and effectiveness of pedicle fixation systems as an adjunct to lumbar fusion for treatment of DDD patients. Table 6 of the said document ("*Effectiveness Data for Posterior Pedicle Screw Spinal Systems for Class III Degenerative Indications*") outlines key manuscripts identified by the Agency. All manuscripts reported

in that table were extracted and carefully reviewed. Of these, prospective studies which focused on circumferential lumbar fusion and pedicle screw fixation or posterolateral fusion with pedicle screw fixation for DDD patients, and which provide, at a minimum, fusion definition and fusion rate results, were selected for the review. Thus, retrospective studies presented in Table 6 (*e.g., Acosta*, *Barnes* and *Al-Masry*), and studies that did not report fusion definition and/or fusion results (*e.g., Glassman*), were excluded. Where applicable, both arms of randomized studies were captured for the literature control.

Next, a computerized search of the National Library of Medicine MEDLINE database utilizing the online search engine PubMed [19] was carried out, to cross-reference these results.

The first search was carried out during November-December 2014, and was complemented by a second search during April-May 2015.

The following search terms were utilized: "fusion" [Title/Abstract], OR "arthrodesis" [Title/Abstract], OR "Interbody" [Title/Abstract], OR "Posterolateral" [Title/Abstract]; AND "lumbar" [Title/Abstract], OR "lumbosacral" [Title/Abstract]; AND "degenerative disc disease" [Title/Abstract], OR "disc degeneration" [Title/Abstract], OR "DDD" [Title/Abstract], OR "spondylosis" [Title/Abstract], OR "back pain" [Title/Abstract].

The searches were limited to articles published in "English" [Language], "Humans" [Medical Subject Headings], NOT "case report" [Title], NOT "cadaver" [Title] OR "anatomical" [Title], NOT "children" [Title] OR "adolescent" [Title], NOT kinematic [Title/Abstract] OR "finite element" [Title/Abstract], from April 1997 to 2015.

A total of 3,990 reports were obtained.

Eleven eligible studies were selected for the analysis, according to the following criteria:

(1) subjects were skeletally matured and had undergone spinal fusion for the lumbar and/or sacral spine;
(2) the intervention included instrumented fusion (interbody and/or posterolateral fusion), in at least one arm of the study;

[19] http://www.ncbi.nlm.nih.gov/pubmed

(3) indications were DDD with or without degenerative spondylolisthesis (up to Grade I);
(4) the study reported at least fusion definition and results of fusion rate;
(5) patients were followed up to at least one year after surgery;
(6) number of patients was at least 20;
(7) manuscripts were given priority if published in high ranking journals and quoted in meta-analysis.
(8) high level of evidence manuscripts (I and II levels).

The flowing manuscripts were selected:

1. Fritzell P, Ha¨gg O, Wessberg P, Nordwall A, and the Swedish Lumbar Spine Study Group. Chronic Low Back Pain and Fusion: A Comparison of Three Surgical Techniques. A Prospective Multicenter Randomized Study from the Swedish Lumbar Spine Study Group. *Spine* 2002;27(11):1131–1141.
2. Zigler J, Delamarter R, Spivak JM, Linovitz RJ, Danielson GO, Haider TT, Cammisa F, Zuchermann J, Balderston R, Kitchel S, Foley K, Watkins R, Bradford D, Yue J, Yuan H, Herkowitz H, Geiger D, Bendo J, Peppers T, Sachs B, Girardi F, Kropf M, Goldstein J. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. *Spine* (Phila. Pa 1976) 2007;32:1155-1162.
3. Anjarwalla NK, Morcom RK, Fraser RD. Supplementary stabilization with anterior lumbar intervertebral fusion--a radiologic review. *Spine* (Phila. Pa 1976) 2006;31:1281-1287.
4. Christensen FB, Hansen ES, Eiskjær SP, Høy K, Helmig P, Neumann P, Niedermann B, Bu¨nger CE. Circumferential Lumbar Spinal Fusion with Brantigan Cage versus Posterolateral Fusion with Titanium Cotrel–Dubousset Instrumentation. A Prospective, Randomized Clinical Study of 146 Patients. *Spine* 2002;2(23):2674–2683.

5. Brantigan JW, Steffee AD, Lewis ML, Quinn LM, Persenaire JM. Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. *Spine* (Phila. Pa 1976) 2000;25:1437-1446.
6. Hackenberg L, Halm H, Bullmann V, Vieth V, Schneider M, Liljenqvist U. Transforaminal lumbar interbody fusion: a safe technique with satisfactory three to five year results. Eur. *Spine J* 2005;14:551-558.
7. Brox JI, Sorensen R, Friis A, Nygaard O, Indahl A, Keller A, Ingebrigtsen T, Eriksen HR, Holm I, Koller AK, Riise R, Reikeras O. Randomized Clinical Trial of Lumbar Instrumented Fusion and Cognitive Intervention and Exercises in Patients with Chronic Low Back Pain and Disc Degeneration. *Spine* 2003;28:1913-1921.
8. Delamarter R, Zigler JE, Balderston RA, Cammisa FP, Goldstein JA, Spivak JM. Prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement compared with circumferential arthrodesis for the treatment of two-level lumbar degenerative disc disease: results at twenty-four months. *J Bone Joint Surg*. *Am*. 2011;93:705-715.
9. Christensen FB, Hansen ES, Laursen L, Thomsen K, Bu¨nger CE. Long-Term Functional Outcome of Pedicle Screw Instrumentation as a Support for Posterolateral Spinal Fusion Randomized Clinical Study With a 5-Year Follow-up *Spine* 2002;27(12):1269–1277.
10. Narayan P, Haid RW, Subach BR, Comey CH, Rodts GE**.** Effect of spinal disease on successful arthrodesis in lumbar pedicle screw fixation. *J Neurosurg Spine* 2002;97:277–280.
11. Arnold PM, Robbins S, Paullus W, Faust S, Holt R, McGuire R. Clinical outcomes of lumbar degenerative disc disease treated with posterior lumbar interbody fusion allograft spacer: a prospective, multicenter trial with 2-year follow-up. *Am. J Orthop*. (Belle Mead NJ.) 2009;38, E115-E122.

Data from the studies was extracted from full text articles and is summarized in the tables presented in **Appendix B**, in accordance with the requirements of the "*FDA Guidance Document for the Preparation of IDEs for Spinal Systems; issued on January 13, 2000*".
It is noted, that where an article describes a randomized clinical trial (RCT), only the study arm/s regarding circumferential fusion and pedicle screw and/or posterolateral fusion with pedicle screw was taken for the following analysis.
Please note, that in order to prevent misinterpretation, whenever possible the text in the fields of the tables in **Appendix B** was copied from the articles, to use the exact wording used by the authors.

The following paragraphs display the results regarding fusion rate, pain (VAS), function (ODI), and safety (adverse events), as presented in the literature control manuscripts (and in the FDA Executive Summary).

A. Fusion

The following table summarizes the **fusion rates**, as described in ten of the 11 articles referenced above. One study (*Arnold*) was not included in the fusion analysis due to discrepancies in fusion rates reported in the article. Please see detailed explanation in **Appendix B**, page 65.

A total of ten level I and II studies (556 patients) reported radiographic fusion outcome for DDD patients who underwent circumferential lumbar arthrodesis with pedicle screws, or posterolateral fusion with pedicle screws, and are used as historical controls.
Nine of those ten studies reported fusion outcome for homogenous cohorts or sub-cohorts (*i.e.*, stratified for DDD patients) using x-ray methods and are therefore analogous to the subject IDE.
In four studies (*Brantigan, Christensen*, *Christensen* II and *Brox*), subgroup stratification for single- and double level was not provided for fusion outcome parameter. One study (*Delamarter*) report fusion rates for two level surgery DDD cohort.

In one study (*Hackenberg*), the results refer to a mixed cohort (DDD and isthmic spondylolisthesis). Nevertheless, most of the patients were DDD patients, and as the non-stratified fusion rate is similar to studies evaluating only DDD patients, it is believed the results of these studies are appropriate to be included in the control group as well. Therefore, this study can also be included when determining the control fusion rate.

Several of the studies evaluated fusion using tools and definitions less rigorous than those suggested for the proposed IDE study (*e.g.,* without flexion-extension radiographs, and thus with no motion assessment). Therefore, the reported fusion rates of those articles may be regarded as worst case for the purpose of comparison. On the other hand, one study (*Anjarwalla*) used thin cut CT to evaluate fusion, which is expected to yield a slightly lower fusion rate. Although the proposed study uses radiographs to assess fusion, both studies use x-rays to assess fusion. Therefore, the slight difference in imaging modalities does not preclude using the results of the study when determining the control fusion rate.

Please note, that the ten studies utilized autogenous bone graft (mainly iliac crest bone graft), which is associated with higher fusion rates than allograft.

Overall, the compilation of these ten articles, reporting fusion results for a total of 556 DDD patients, provides for reliable control group for comparison of fusion rate. It is emphasized that all of the mentioned studies were regarded as appropriate for the review of DDD patients in the FDA Executive Summary, and thus are reported in Table 6 of the said document.

Seven of the ten studies report fusion rates at two years, while two studies (*Christensen* and *Nrayan*) reports rates at one year. One study (*Christensen* II) reports fusion rate at both one and two years. Slightly higher fusion rates are expected at two years as compared to one year. As the fusion rate of the subject device is assessed at one year, it is either analogous or worst-case compared to the literature control. Therefore, despite differences in time points, a valid comparison can be made.

Fusion success rates reported in the ten manuscripts, and calculated weighted average of values, are presented in the tables below. The weighting factor is the number of patients in each study.

Table 2: Literature Control - Radiographic Fusion Outcome

	Single Level	Double Level	Procedure	Diagnosis	Cohort Size	Fusion N_{fused}/N_{chhort}		Fusion Rate [%]
Fritzell 2002 (Arm I)	N_{24}=43	N_{24}=21	ALIF or PLIF + PLF + PSS	DDD	N_{24}=64	58	64	**91 2 years**
Fritzell 2002 (Arm II)	N_{24}=35	N_{24}=27	PSF + PSS	DDD	N_{24}=62	54	62	**87 2 years**
Zigler 2007	N_{24}=69	-	ALIF + PLF + PSS	DDD	N_{24}=69	67	69	**97 2 years**
Anjarwalla 2006	N_{24}=14	N_{24}=10	ALIF + PLF + PSS	DDD	N_{24}=24	21	24	**88** § **2 years**
Christensen ‡ **2002 (Arm I)**	Cohort comprised 1-2 level surgeries; data not stratified		ALIF + PLF + PSS or facet joints screws	DDD	N_{12}=22 (only DDD patients) ☼	19	22	**86 1 year**
Christensen ‡ **2002 (Arm II)**	Cohort comprised 1-2 level surgeries; data not stratified		PLF + PSS	DDD	N_{12}=22 (only DDD patients) ♦	19	22	**86 1 year**
Brantigan ‡ **2000**	Cohort comprised 1-3 level surgeries; data not stratified		PLIF + PLF + PSS	DDD	N_{24}=91	82	91	**90** ♣ **2 years**
Hackenberg * 2005	N_{36}=39	N_{36}=11 (2-level) N_{36}=2 (3-level)	TLIF + PLF + PSS	30 DDD + 22 isthmic spondyloli-sthesis	N_{36}=52	46	52	**89 2 years**
Brox ‡ **2003**	Cohort comprised 1-2 level surgeries; data not stratified		PLF + PSS	DDD	N_{12}=35	29	35	**84 2 years**
Delamarter 2009	-	N_{24}=61	ALIF + PLF + PSS	DDD	N_{24}=61	47	61	**77 2 years**
Christensen II ‡ **2002**	Cohort comprised 1-2 level surgeries; data not stratified		PLF + PSS	DDD	N=20	15	20	**77 1 year**
Naryan 1997	N34=$_{12}$	-	PLF + PSS	DDD	N_{12}=34	31	34	**91 1 year**

* Results refer to several diagnoses. In addition, subgroup stratification for single- and double level (or more) is not provided for fusion outcome parameter.

‡ Subgroup stratification for single- and double level (or more) is not provided for fusion outcome parameter.

☼ The number of DDD patients available for radiographic evaluation is assumed to be 22. The authors report the number of operated patients (73) and their stratification to the following 3 sub-groups: 24 with primary degeneration; 25 with secondary degeneration; and 24 with isthmic spondylolisthesis. Of these 73 patients, radiographic evaluation was performed for 67 patients (no stratifications to the 3 sub-groups). As the number of patients in each of the 3 sub-groups is similar, we arbitrary decided that 2 patients in each group were not available for the radiographic evaluation.

♦ The number of DDD patients available for radiographic evaluation is assumed to be 22. The authors report the number of operated patients (72) and their stratification to the following 3 sub-groups: 19 with primary degeneration; 27 with secondary degeneration; and 27 with isthmic spondylolisthesis. Of these 72 patients, radiographic evaluation was performed for 57 patients (no stratifications to the 3 sub-groups). As the number of patients in each of the 3 sub-groups is similar, we arbitrary decided that 5 patients in each group were not available for the radiographic evaluation.

§ Per CT.

♣ According to FDA Summary of Safety and effectiveness.

As shown in the table, the fusion rates reported in the literature control range from **77%** to **97%**.

The following sections provide for calculation for the control group fusion rates.

For dichotomy (binary) outcome parameters, the following formulas were used to compute weighed average and standard deviation:

$$Weighted\ average = \frac{n1p1 + n2p2 \ldots nXpX}{n1 + n2 \ldots nX}$$

$$variance = \frac{n1p1q1 + n2p2q2 \ldots nXpXqX}{(n1 + n2 \ldots + nX)2}$$

$$SD = \sqrt[2]{variance}$$

Where:

p = success probability (fusion)

q = failure probability (1-P)

Weighted average:

=0.8779

Standard deviation:

= 0.0136

Table 3: Literature Control - Average Fusion Rate

Number of Manuscripts	Number of Patients	Single Level	Double Level	1 or 2 Level	Weighted Average	SD	Range	
10 (a total of 12 study arms)	488/556	234	195	127	**87.79%**	**1.36%**	77%	97%

To conclude, the average fusion rate for the control group is **87.79 % ± 1.36%**.

A recently published systematic literature review, which analyzed published literature to evaluate the efficacy of lumbar arthrodesis for DDD patients [20], reported "*As a whole, these 12 studies including 1420 fusion patients showed…., the fusion rate was **89.3%** (95% CI, 84.4–94.2*)" [*emphasis added*]. This correlates with the above values.

It should be stressed that part of the studies reported in the literature used less stringent definitions of fusion than those used in various IDE studies for lumbar fusion, including the suggested IDE. For example, fusion rate of 74.6% was reported for the control group (Silhouette Spinal Fixation System) of the Dynesys Spinal System (Zimmer Spine) (P070031), and a fusion rate of 88.1% was reported for the control group (LT-CAGE Lumbar Tapered Fusion Device filled with ICBG) in P000058. Use in less stringent fusion definitions results in the relatively higher fusion rates reported in the literature. Further, per FDA's recommendations, the definition of the angular motion in the proposed IDE is even more rigorous (*i.e*. 3° versus 5°) than the fusion definition of previous IDE studies.

B. ODI

The following tables summarize the **ODI results**, as described in the articles referenced above.

The ODI (also known as the Oswestry Low Back Pain Disability Questionnaire) is a validated tool used to measure a patient's level of pain and functional disability. The test is considered the 'gold standard' of low back functional outcome tools [21]. Past IDE studies success criterion required 15-point improvement.

A total of five level I and II studies (321 patients) from the control group reported the outcome of the Oswestry Disability Index (ODI) for DDD patients who underwent lumbar arthrodesis with pedicle screws, and are used as historical controls.

[20] Phillips FM1, Slosar PJ, Youssef JA, Andersson G, Papatheofanis F.Spine (Phila Pa 1976). Lumbar Spine Fusion For Chronic Low Back Pain Due TO Degenerative Disc Disease: A Systematic Review. *Spine* 2013;38(7):E409-422.

[21] Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine 2000 Nov 15;25(22):2940-52.

One study (*Zigler*) reported outcome for homogenous single level DDD cohort and is, therefore, directly comparable to the proposed IDE study. In three studies (*Fritzell, Hackenberg* and *Brox*), subgroup stratification for single- and double level DDD was not provided for ODI outcome parameter (please note, that *Hackenberg et al.* provide ODI results stratification for one/two-level for all subjects (a total of 30 DDD patients and 22 isthmic spondylolisthesis patients); the overall ODI improvement is relatively similar for patients undergoing one- or 2-level surgery). *Delamarter* reported outcome for homogenous 2-level DDD cohort. Overall, the final ODI value for all five studies is similar, suggesting that the differences in patient population do not preclude their pooling to enable a general comparison between the literature control and IDE study group.

Results from three studies (*Zigler, Hackenberg* and *Delamarter*) that evaluated ODI at one and two-year follow-up visits suggest that the number of patients that experienced a clinically meaningful change in ODI does not change significantly from one to two years, allowing pooling of both one and two year results.

ODI outcome reported in the five manuscripts, and calculated weighted average of values, are presented in the tables below. The weighting factor was the number of patients in each study.

Table 4: Literature Control - Oswestrey Disability Index (ODI) Outcome

	Single Level	Double Level	Procedure	Diagnosis	Cohort Size	ODI Baseline	ODI 12 Months	ODI 24 Months	Improvement (Δ) (ODI_{bl}-$ODI_{last\ f.\ u.}$)	% Improvement (Δ ODI/ ODI_{bl})
Fritzell 2002 (Arm I)	N_{24}=43 *	N_{24}=21 *	ALIF or PLIF + PLF + PSS	DDD	N_{24}=65*	47.3 ± 10.9	-	38.5 ± 18.9	8.8	(19%)
Fritzell 2002 (Arm II)	N_{24}=35♦	N_{24}=27♦	PSF + PSS	DDD	N_{24}=59♦	48.4 ± 11.6	-	33.6 ± 17.9	14.8	(30%)
Zigler 2007	N_{24}=71	-	ALIF + PLF + PSS	DDD	N_{24}=71	62.7 ± 10.3	40.7	39.8 ± 24.3	22.9	(37%)
Hackenberg 2005	No level stratification		TLIF + PLF + PSS	DDD	N_{36}=30	58.4 ± 18.4	37.5 ± 19.3	37.0 ± 24.8	21.4	(37%)
Delamarter 2009	-	N_{24}=61	ALIF + PLF + PSS	DDD	N_{24}=61	64.8 ± 9.5	41.1 ± 23.0	38.7 ± 24.1	26.1	(40%)
Brox 2003	No level stratification		PLF + PSS	DDD	N_{12}=35	42.0 ± 11.0	26.4 ± 16.4	-	15.6	(37%)

* The ODI evaluation was conducted for 65 patients, however the stratification to one and two-level was given to 64 patients that were radiographically evaluated.
♦ The ODI evaluation was conducted for 59 patients, however the stratification to one and two-level was given to 62 patients that were radiographically evaluated.

Table 5: Literature Control - ODI Reference Results

	Points Range	Number of Manuscripts	Number of Patients	Weighted Average
12m Δ Improvement (single level)	22.0	1	71	22.0
24m Δ Improvement (single level)	22.9	1	71	22.9
12m Δ Improvement (double level)	23.7	1	61	23.7
24m Δ Improvement (double level)	26.1	1	61	26.1
12m Δ Improvement (1 & 2 levels)	20.9 – 23.7	4	197	23.4
24m Δ Improvement (1 & 2 levels)	8.8 - 26.1	4 (total of 5 study arms)	286	18.5

As can be seen, the similar values were reported for one- and 2-level and for one- and two years, justifying the pooling of the results.

Number of Manuscripts	Number of Patients	Weighted Average Improvement (Δ)	Weighted Average Improvement (%)	Range	
5 (a total of 6 study arms)	321	18.22	32.63%	8.8 (19%)	26.1 (40%)

In addition, the recently published systematic literature review (Phillips *et al*.) mentioned above analyzed published literature to evaluate the efficacy of lumbar arthrodesis for DDD patients, reported "*As a whole, these 12 studies including 1420 fusion patients showed a weighted average improvement in ODI function of **24.7** ± 6.2/100 (47.2% change; 95% CI, 41.3–53.1)*" [*emphasis added*]. This correlates with the values listed in the tables.

C. VAS Pain

The following table summarizes the **VAS (pain) results**, as described in the articles referenced above.

A total of five level I & II studies (321 patients) from the control group reported pain outcome for DDD patients who underwent circumferential lumbar arthrodesis with pedicle screws, and are used as historical controls.

The Visual Analog Scale (VAS) for Pain is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations [22]. It is a continuous scale comprised of a horizontal visual analog scale of 100 mm length. It is anchored by two verbal descriptors (No Pain and Severe Pain). Values here refer to back pain as VAS leg pain is reported in only one study (*Fritzell*). Please note that also in Frizell study the back pain was the dominant pain component (compared to leg pain).

One study (*Zigler*) reported VAS pain outcome for homogenous single level DDD cohort and was therefore analogous to the proposed IDE study. In the three studies (*Fritzell* and *Hackenberg* and *Brox*), subgroup stratification for single- and double level was not provided for VAS pain outcome parameter. Please note, that *Hackenberg et al* provided VAS (pain) results stratification for one/two-level for all subjects (a total of 30 DDD patients and 22 isthmic spondylolisthesis patients); the overall VAS improvement is relatively similar for patients undergoing one- or 2-level surgery). Overall, the final VAS score for most of the studies is similar, suggesting that the differences in patient population do not preclude their pooling to enable a general comparison between the literature control and IDE study group.

[22] Mc Cormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. *Psychol Med* 1988;18:1007–1019.

As can be seen in the table below, VAS improvement results for the same patients at 12 months and 24 months postoperatively are very similar and results can be pooled from one to two years.

VAS pain outcome reported in the five manuscripts and calculated weighted average of values are presented below. The weighting factor was the number of patients in each study. Where applicable (*Hackenberg*), VAS score results were converted to a 100-point score, for consistent interpretation.

Table 6: Literature Control - Visual Analogue Scale (VAS) Outcome

	Single Level	Double Level	Procedure	Diagnosis	Cohort Size	VAS Baseline	VAS 12 m	VAS 24 m	Improvement (Δ) ($VASI_{bl}$-$VAS_{last\ f.u.}$)	% Improvement (Δ VAS/VAS_{bl})
Fritzell 2002 (Arm I)	N_{24}=43*	N_{24}=21*	ALIF or PLIF + PLF + PSS	DDD	N_{24}=65*	65.6 ± 15.2	-	45.7 ± 26.7	19.9	(30%)
Fritzell 2002 (Arm II)	N_{24}=35♦	N_{24}=27 ♦	PSF + PSS	DDD	N_{24}=59 ♦	63.3 ± 13.3	-	40.4 ± 23.9	22.9	(36%)
Zigler 2007	N_{24}=71	-	ALIF + PLF + PSS	DDD	N_{24}=71	75 ± 14.6	42 ± 28	43 ± 31.6	32	(43%)
Hackenberg 2005	No level stratification		TLIF + PLF + PSS	DDD	N_{36}=30	83 ± 26	45 ± 23	48 ± 28	35	(42%)
Delamarter 2009	-	N_{24}=61	ALIF + PLF + PSS	DDD	N_{24}=61	74.7 ± 13.6	40.3 ± 27.9	38.4 ± 29.8	36.3	(49%)
Brox 2003	No level stratification		PLF + PSS	DDD	N_{12}=35	62.1 ± 14.5	39.4 ± 25.5	-	22.7	(37%)

* The ODI evaluation was conducted for 65 patients, however the stratification to one and two-level was given to 64 patients that were radiographically evaluated.

♦ The ODI evaluation was conducted for 59 patients, however the stratification to one and two-level was given to 62 patients that were radiographically evaluated.

Table 7: Literature Control - VAS Reference Results

	Point Range	Number of Manuscripts	Number of Patients	Weighted Average
12m Δ Improvement (single level)	33	1	71	33
24m Δ Improvement (single level)	32	1	71	32
12m Δ Improvement (double level)	34.4	1	61	34.4
24m Δ Improvement (double level)	36.3	1	61	36.3
12m Δ Improvement (1 & 2 levels)	22.7 - 38	4	197	32.4
24m Δ Improvement (1 & 2 levels)	19.9 – 36.3	4 (total of 5 study arms)	286	28.6

As can be seen, the overall patient population had a VAS improvement of around 30 points. In addition, similar values were reported for one- and 2-level and for one- and two years, justifying the pooling of the results.

Number of Manuscripts	Number of Patients	Weighted Average Improvement (Δ)	Weighted Average Improvement (%)	Range	
5 (a total of 6 study arms)	321	27.96	39.47%	19.9 (30%)	36.3 (49%)

In addition, Phillips *et al*. published recently systematic literature review, which analyzed published literature to evaluate the efficacy of lumbar arthrodesis for DDD patients, and reported that "*As a whole, these 12 studies including 1420 fusion patients showed a weighted average improvement in back pain of 36.5 ± 17.2/100 points (43.3% change; 95% CI, 31.5–55.1)*."

D. Adverse Events

The description of adverse events in the manuscripts used for the literature review is not uniform; some authors describe the adverse events in detail, while other do not (see the tables in **Appendix B**, listing all adverse events mentioned in the control articles). In light of this limitation, the Company used the safety data provided in Table 7 of the FDA's Executive Summary for DDD patients (n=1,350; complications=921; re-operation=814). The relevant section (*i.e.*, DDD patients) of the said table is presented below:

ADEVERSE EVENT	RATE
Screw Malposition	0.5%
Screw Loosening	0.4%
Rod/Plate/Screw Breakage	1.3%
Construct Disassembly	0.1%
Bone Fracture	-
Graft Settling/Displacement	0.1%
Pseudoarthrosis	5.9%
Bleeding/Vascular Injury	0.7%
Neurologic Injury	0.8%
Nerve Root injury	0.3%
Spinal Cord Injury	0.0%
Back/Leg Pain (Radiculopathy)	0.7%
Dural Tear/CSF Leak	1.0%
Wound problems *(*Hematoma/Seroma*)*	0.3%
Infection/Sepsis	3.9%
Superficial	2.6%
Deep	0.9%
Skin Irritation	0.3%
Cardiac	0.2%
Respiratory	0.4%
Gastrointestinal	0.3%
Urologic/Reproductive	0.1%
Reoperation/Revision	10.9%
Removal of Hardware	5.5%

It is not possible to simply sum the event rates for each adverse event to establish a control adverse event rate for several reasons. The table above does not specify the adverse event severity or device relatedness. Further, the same type of adverse event, such as skin irritation, may be categorized with various degrees of severity depending on the actions taken to resolve

the event. In addition, it is possible that several adverse events occurred in the same patient, which means summing the rates would lead to an erroneously high adverse event rate.
Therefore, the Company believes that a conservative estimate of relevant adverse events can be obtained by summing all device-related serious adverse events, all reoperations/revisions and all neurological injuries.
Therefore, the rate of failure of devices in the control group for safety reasons is 13.5% which includes all device-related serious adverse events (including screw loosening, implant breakage and construct disassembly), reoperations/revisions and neurologic injuries.

5.3 INCLUSION CRITERIA

A subject will be considered eligible for inclusion in this study only if all of the following criteria apply:

1. Subject has degenerative disc disease (DDD) at one level, from L2 to S1 vertebrae, with up to Grade I spondylolisthesis.

   DDD is defined as back pain and/or radicular leg pain with degeneration of the disc confirmed by patient history, radiographic studies, and physical examination, with one or more of the following factors (as measured radiographically, either by CT, MRI or plain film, myelography, discography, *etc*.):

   - osteophyte formation of facet joints or vertebral endplates;
   - decreased disc height, on average by > 2 mm;
   - scarring/thickening of ligamentum flavum, annulus fibrosis, or facet joint capsule;
   - herniated nucleus pulposus;
   - facet joint degeneration/changes;
   - vacuum phenomenon.
2. Subject is candidate for single level intervertebral fusion, with or without posterolateral fusion, with implantation of intervertebral body fusion device and supplemental fixation.
3. Subject age is between 21 – 72 years, and subject is skeletally mature.

4. Pre-operative low back and/or leg/s pain (debilitating pain that causes a significant disturbance of the routine daily physical activities) ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS).
5. Pre-operative Oswestry Disability Index (ODI) score ≥ 40 percentage-point, indicating at least moderate disability (interpreted as moderate/severe disability).
6. Low back and/or leg/s pain is unresponsive to prior non-surgical management for a minimum of six months. Non-operative treatment includes pain medication, physical therapy and/or injections.
7. Patient must understand and sign the informed consent.
8. Patient is willing and able to meet the proposed follow-up schedule including return to follow-up visits and complete necessary study paperwork.
9. Patient is willing and able to follow the postoperative management program.

5.4 EXCLUSION CRITERIA

A subject will not be considered eligible for inclusion in this study if any of the following criteria applies:

1. Previous fusion or fusion attempts, including anterior fusion or posterolateral fusion, at the index level.
2. Previous fusion or fusion attempts at the adjacent levels.
3. Prior decompression procedures that include removal of soft and bone tissue at the index or adjacent levels.
4. Patient is not skeletally mature.
5. Degenerative spondylolisthesis greater than Grade I.
6. Spinal instability at the index level with ≥ 3 mm translation and/or ≥ 5 degrees angulation. Determination of instability will be assessed using flexion/extension lateral view radiographs.
7. Isthmic spondylolisthesis.

8. Radiographically confirmed moderate or severe spinal stenosis with associated neurogenic claudication.

   Definitions:

   - Radiographically confirmed moderate/severe stenosis is defined as reduction of >50% of central and/or foraminal canal diameter compared to the adjacent uninvolved levels.
   - Neurogenic claudication is leg, groin, or buttock pain and/or numbness that worsens with walking or erect posture and is relieved with flexion of the spine.

9. Systemic infection or infection at the site of surgery.
10. Metabolic bone disease, such as osteopenia, osteoporosis, and osteomalacia. A screening Questionnaire for osteoporosis, 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 measured T-score less than or equal to -2.5 (WHO definition).
11. History of Paget's disease or other bone pathologies, whether acquired or congenital, including renal osteodystrophy, untreated or uncontrolled hyperthyroidism, hypothyroidism, or hyperparathyroidism, Ehrlers-Danlos-syndrome, osteogenesis imperfecta, achondroplasia, tuberculosis.
12. Personal and/or familial history NF2, and/or spinal tumor.
13. Ankylosing spondylitis.
14. Diffuse idiopathic skeletal hyperostosis (DISH) syndrome.
15. Active hepatitis (viral or serum) or HIV positive, renal failure, systemic lupus erythematosus, or any other significant medical conditions which would substantially increase the risk of surgery.
16. Immune deficiency disease.
17. Patient is receiving immunosuppressive or long-term steroid therapy.
18. Active malignancy or other significant medical comorbidities.
19. All concomitant diseases that can jeopardize the functioning and success of the patient.

20. Allergy to any component of the investigational device, including carbon fiber-reinforced polyetheretherketone (CFR-PEEK), titanium, and tantalum.
21. Pregnancy, or female subject interested in become pregnant during the duration of the study.
22. Current chemical dependency (*e.g.,* drug and/or alcohol abuse, according to DSM-V definition), as well as those with a history of such abuse.
23. Uncontrolled depression, psychosis, or other symptoms of a mental disorder that, in the investigator's opinion, likely would make the subject unable to comply with the study procedures and could affect the study outcome.
24. Treatment with drugs that may interfere with bone metabolism, such as glucocorticosteroids, calcitonin, bisphosphonates, bone therapeutic doses of fluoride, bone therapeutic doses of vitamin D or vitamin D metabolites, and treatment by chemotherapy.
25. Morbid obesity (BMI $\geq$ 40).
26. Current smokers (including 3 months prior to surgery).
27. Scoliosis, Cobb angle greater than 11°.
28. Vertebral fractures.
29. Severe muscular, neural or vascular diseases that endanger the spinal column.
30. Missing bone structures, due to severely deformed anatomy or congenital anomalies, which make good anchorage of the implant impossible.
31. Paralysis.
32. Current use of other investigational drug or device.
33. The patient is involved in a worker's compensation case or spine-related litigation.
34. The patient is a prisoner.

Note: The time elapses between the diagnostic studies required for entry and enrolment into the study is limited to up to three months.

5.5 NUMBER OF PATIENTS AND PATIENT SELECTION

Patients Number:

A total of 55 patients will be recruited for the study (up to 15 subjects will be recruited in this site). Their results will be combined with an additional 45 patients from the ongoing OUS

study, the details of which are presented in the Investigator Brochure. When combined with the patients from the ongoing OUS study, 55 patients was deemed sufficient for this confirmatory, single-arm study. Therefore, the total effective sample size is about 100 patients.

Patients Selection:

In order to be included in this study, patients will have to fulfill all the Inclusion Criteria and none of the Exclusion Criteria, as well as to sign and date the Informed Consent Form.

All patients' full medical history will be recorded and all patients will undergo a complete general physical and neurological examination. Plain A-P and lateral X-Ray films, as well as lateral flexion-extension X-Rays, will be performed prior to surgery.

Neurological examination will be performed to confirm that the patient' clinical signs and symptoms are consistent with the baseline disease level/s demonstrated per imaging.

An anesthesiologist will assess the patient for general anesthesia, according to the routine practice.

5.6 STUDY SITES

Up to eight sites may participate in the study. At least two sites will be in the USA, recruiting at least 30 patients.

5.7 STUDY DURATION

The study is expected to last up to 36 months (total duration), including patient enrollment and a post-operative follow-up period of 24 months per subject.

The primary safety and effectiveness analyses will be performed at 24 months. The collected information will be submitted to the FDA as part of a 510(k) Premarket Notification after all patients have completed 24 months of follow-up. In case of satisfactory results, the Company intends to submit the results of the study to the FDA, after all patients have completed the 12 months follow-up, as part of a Premarket Notification (510(k)). It is emphasized, that all patients will be additionally followed at 24-month time point, and afterwards annually, until the last patient completed 2-year follow-up. It is noted, that at the time all subjects from IDE

study reach 12-month follow-up, it is expected that 2-year supportive data from the original, ongoing OUS clinical study with the investigational device will be available.

Patients will be followed and assessed both clinically and radiographically after surgery at follow-up visits.

Evaluation time points shall be conducted at the following intervals:

- Preoperatively (with up to 3 months between the diagnostic studies to enrolment);
- Operatively;
- Postoperatively, at discharge from hospital;
- Postoperatively, at 6 weeks ± 2 weeks from surgery;
- Postoperatively, at 3 months ± 2 weeks from surgery;
- Postoperatively, at 6 months ± 1 month from surgery;
- Postoperatively, at 12 months ± 2 months from surgery.
- Postoperatively, at 24 months ± 2 months from surgery.

Afterwards, subjects will be clinically evaluated annually, until the last patient has completed 2-year follow-up.

At baseline, discharge, and at follow-up sessions, radiographic evaluation, pain and functionality evaluations, and subject's overall well-being assessment shall be performed. Assessment of subject' satisfaction shall be performed postoperatively, starting at 6-week follow-up.

Complications/adverse events shall be evaluated operatively and at each evaluation time points, as well as throughout the study.

Refer to **Sections 5.9** and **5.10** for a detailed schedule and assessment description, respectively.

5.8 MISSING DATA

Incomplete information may be available for a subject for various reasons:

- Subject stopped participation in the study at its own request;
- Continuing the follow-up is not possible/subject lost to follow-up;

- Subject stopped participation in the study at the Investigator's discretion.

In general, in cases where information will be available for a certain missing data point from a previous and from the next follow-up, an interpolation of the values shall be performed. Missing data from patients that were lost to follow-up will be handle by "last value carried forward" approach (*i.e.*, the last value obtained from a subject will be used for the analysis).

5.9 PROCEDURES

5.9.1 PREOPERATIVE MANAGEMENT

a. The Investigator will select the subjects according to the inclusion and exclusion criteria, as described in **Sections 5.3** and **5.4**, respectively.
b. The Investigator will be acquainted with the technique and instrumentation required for the procedure. Training will be provided by the Sponsor or its authorized representatives in accordance with the Training Protocol (**Appendix C**).
c. The Investigator will be familiar with the Protocol of the clinical trial.
d. Signed written Informed Consent must be obtained for all subjects.
e. The patients shall be instructed to refrain from the use of NSAIDS for two weeks prior to surgery.
f. All female subjects who are of child bearing age should present a negative beta-HCG blood (pregnancy) test or submit a signed statement that she is using at least one conventional contraceptive method and that to the best of her knowledge she is not pregnant. Such woman shall be informed of the risks involved in participating in the study while pregnant and cautioned to inform the study personnel if she becomes pregnant during the timeframe of the study.

Pre-procedure assessment will be conducted according to the outline provided in the Case Report Forms (CRFs) booklet.

Pre-procedure examination includes (refer also to **Table 8** below):

- Demographic data
- Full medical history, including concomitant medications

- Physical examination
- Neurological examination
- X-Ray evaluation

The results of the said examinations shall be recorded.

During the pre-operative session, the following forms shall be completed (refer also to **Table 9** below):

- Pre-operative CRF
- Patient baseline questionnaires (Visual Analogue Scale (VAS, for back and leg pain assessment), Oswestry Disability Index (ODI), and 12-Item Short Form Health Survey (SF-12)

5.9.2 SURGICAL PROCEDURE

The surgical procedure is described in the system Surgical Technique (**Appendix A**).

The Operative CRF shall be completed.

In case of an adverse event, the appropriate CRF should be filled.

5.9.3 POSTOPERATIVE MANAGEMENT

In general, postoperative management shall be conducted according to the description in the CRFs.

Immediate post-operative management should be as per routine hospital standard of care.

Prior to ***discharge***, the following examinations/tests shall be performed (refer also to **Table 8** below and to the description in the Discharge CRF):

- Physical examination
- Neurological Examination
- X-Ray evaluation

The results of the said examinations shall be recorded on the Discharge CRF.

In addition, the patient shall be interviewed regarding adverse events; in case of an adverse event, the appropriate form should be filled.

The patients shall be instructed to refrain from the use of NSAIDS for three months post-operatively.

During ***follow-up visits***, the following post-operative examinations/tests shall be performed (refer also to **Table 8** below and to the description in the post-operative CRFs):

- Physical examination
- Neurological Examination
- X-Ray evaluation

The results of the said examinations shall be recorded.

At every follow-up visits the following forms shall be completed (refer to **Table 9**):

- Post-operative CRF
- Patient follow-up questionnaires (VAS (pain), ODI, SF-12, VAS (donor site pain, if applicable), and VAS (satisfaction))

In addition, the patient shall be interviewed at each follow-up visit regarding adverse events, and the appropriate form should be filled. If a non-scheduled postoperative visit results from such an event, it should be noted on the form.

Table 8 below lists the assessment schedule and examinations.

Table 8: Assessment Schedule

Description	Pre-Procedure	Operation	Discharge	6 Weeks Visit	3 Months Visit	6 Months Visit	12 Months Visit	24 Months Visit	Annual Visit §	Unscheduled Visit
Inclusion/Exclusion Criteria	√									
Informed Consent (signed & dated)	√									
Demographic & Medical History	√									
Physical Examination	√		√	√	√	√	√	√	√	√
Neurological Examination	√		√	√	√	√	√	√	√	√
X-Rays (AP, Lateral and Flexion/Extension)	√	Fluoroscopy	√ *	√ *	√ *	√	√	√	√	√ **
Patient Questionnaires (VAS (Pain), ODI, SF-12, VAS (Satisfaction))	√ ¤			√	√	√	√	√	√	
CT Scan						√ ¥	√ ¥	√ ¥	√ ¥	
AE Recording		√	√	√	√	√	√	√	√	√

§ Will be performed after the 24-month follow-up, until the last patient completes 2-year follow-up.
* Except for flexion/extension X-rays.
** Will be performed only if required according to the physician discretion.
¤ Except for patient satisfaction VAS.
¥ CT scan will be conducted for patients in whom bridging bone status cannot be determined in X-Rays.

Table 9 below lists the Questionnaires and Forms that need to be completed during baseline and postoperatively evaluations.

Table 9: Forms/Questionnaires to be Completed at Pre-Op. and Follow-Up Visits

Form Type	Pre-Operation	Operation	Discharge	6 weeks Post-Op.	3 Months Post-Op.	6 Months Post-Op.	12 Months Post-Op.	24 Months Post-Op.	Annual Visit *	Unscheduled Visit
Pre-Op. CRF (Enrollment and Baseline Forms)	√									
Operative CRF		√								
Discharge CRF			√							
Post-Op. CRF				√	√	√	√	√	√	
Unscheduled Visit CRF										√
Medications CRF – Follow Up			Medications Form should be completed at discharge and follow-up sessions, in case any concomitant medication was used during hospitalization or since last visit, respectively							
Adverse Event CRFs (AEs, SAE, Additional Surgery)		When applicable								
Protocol Deviation		When applicable								
Conclusion CRF			At 24 Months, or when applicable							
VAS (Pain), ODI & SF-12	√			√	√	√	√	√	√	
VAS (Donor Site Pain), if applicable				√	√	√	√	√	√	
VAS (Satisfaction)				√	√	√	√	√	√	

* Will be performed annually after reaching the 24-month follow-up, until the last patient completes 2-year follow-up

Subjects who shall withdraw from the study will have the Conclusion CRF completed for them upon their request to withdraw from the study. The reason for withdrawal and any alternative treatment suggested to the patient shall be indicated on the form. In case a subject who is lost to follow up returns at a later stage, this will be indicated as a remark on the Conclusion CRF along with the reason the patient missed the previous follow-up session(s).

5.10 EVALUATION OF PRIMARY OUTCOME MEASURES

5.10.1 FUSION EVALUATION

Fusion will be evaluated radiographically, by A-P, lateral and flexion/extension X-Rays (flexion/extension films will be used for the assessment of angular and translational motions). As detailed below, in case of inconclusive findings regarding bridging bone, a CT scan will also be performed, and evaluated by the core lab.

Fusion assessment shall be made postoperatively, starting at 6 months and at each follow-up session afterwards.

Each fusion area (between the endplates, at right posterolateral, and at left posterolateral, as applicable) will be assessed separately.

All radiographs will be read by two independent, board-certified, radiologists from Medical Metrics, Inc., with experience in musculoskeletal imaging, blinded to clinical outcomes, and without any financial interest in CarboFix Orthopedics, to ensure consistent reading of the radiographs and elimination of bias. In the case of a disagreement between the two radiographic assessors, a third independent reviewer will evaluate the radiographic images to adjudicate the findings.

Please refer to **Appendix D** for radiographic protocols, including Image Acquisition Protocol, Image Transfer Protocol, and Radiographic Evaluation Protocol. All said protocols were provided to CarboFix by Medical Metrics, Inc.

Fusion Radiographic Patient Success is defined when all the following radiographic endpoints are met at 24 months:

a. Angular motion < 3º; AND
b. Translational motion < 3 mm; AND
c. Presence of continuous bridging bone between the involved motion segment, *i.e.*:
    - Presence of interbody (between endplates) bridging bone and absence of radiolucency > 50%; OR
    - Presence of left posterolateral bridging bone; OR
    - Presence of left posterolateral bridging bone.

Regarding angular motion, reporting of subjects will be provided in the following three groups:

1. those with ≤ 3º total angular motion,
2. those between 3º and 5º of motion, and
3. those with ≥ 5º of motion.

In case bone graft would be placed in the interbody space as well as posterolaterally, on both sides, bridging would be assessed in each of the three areas. Bridging in any one area would be considered adequate to document the presence of affirmative bridging.

Radiolucency will be evaluated as the percent coverage of radiolucent lines along the graft / endplate interface. There will be a single assessment for the superior and inferior bone / graft interfaces combined. Radiolucency will be evaluated primarily from lateral views. The view (neutral, flexion or extension) showing the most severe extent of radiolucency will be used to document the assessment.
Radiolucency will be used to document bone resorption. Particularly in the early stages of healing, poor conformance of the graft with the endplate geometry, *i.e.* poor "fit and fill", will not be identified as radiolucency.

Radiolucency will be graded in accordance with the following definitions:

None: No radiolucent lines along the interbody graft / endplate interface.

Mild: ≤ 25% radiolucent lines along the interbody graft / endplate interface.

Moderate: 26% - 50% radiolucent lines along the interbody graft / endplate interface.

Severe: > 50% radiolucent lines along the interbody graft / endplate interface.

Non-fusion will be indicated in the following cases:
Angular motion ≥ 3° OR translational motion ≥ 3 mm OR absence of continuous bridging bone, *i.e.*:

- Absence of interbody bridging bone and presence of radiolucency >50%; AND
- Absence of left posterolateral bridging bone; AND
- Absence of right posterolateral bridging bone.

Possibly fusion: Patients in whom the status of bridging bone is inconclusive will undergo fine cut CT scan to determine bridging bone and fusion status. At each timepoint, starting at 6 months, any inconclusive X-Rays assessment relates to bridging bone shall be repeated within window, using CT.

Information regarding the CT scans (including the procedures for obtaining and transmitting the CT scans) is presented in the Radiographic Protocol (**Appendix D**).
Definition of bridging bone evaluated in CT scan is as follows (on top of motion evaluated by flexion/extension X-Rays):
Presence of continuous bridging bone between the endplates; or between the right facets, pedicle and/or transverse processes; or between the left facets, pedicle and/or transverse processes, as applicable.

The fusion rate obtained in the study shall be compared to the fusion rates reported in the literature (as summarized in **Section 5.2.1**).

5.10.2 PAIN AND FUNCTION EVALUATION

Pain and functionality will be assessed using dedicated questionnaires.

VAS (Back, Right Leg, and Left Leg Pain): The assessment of pre- and post-operative pain shall be performed using scores determined from measurements of responses to pain question for each location (*i.e.*, low back, right leg, and left leg), provided on a 100 mm Visual Analog Scale (VAS). The anchor points are "No Pain" (0 mm) and "Severe Pain" (100 mm). Patients will be instructed to draw a single line across the scale at the point that best described their level of pain.

The pain VAS assessment will be administered preoperatively as well as at each postoperative visit, starting at 6 weeks.

ODI (Functionality): The Oswestry Disability Index (ODI) will be used to assess function. The ODI questionnaire is based on patient's responses to ten questions, which focus on pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. Each question has six possible answers. The responses to each question ranges from zero to five points. A lower numeric score represents a better pain and disability status regarding that variable (0 points for functionality with no associated pain or no extra pain; 5 points for inability to perform function due to pain). A total ODI score is determined by adding the scores of the individual questions and dividing that total by the maximum possible total score (50 if all questions are answered); this yields a percentage. Therefore, ODI scores shall be presented ranging from 0% to 100%, with a lower percentage indicating less pain and disability.

The ODI questionnaire will be administered preoperatively as well as at each postoperative visit, starting at 6 weeks visit.

<u>Clinically Meaningful Improvements</u> –

- Individual patient clinically meaningful improvement with respect to ***pain*** is defined as postoperative improvement at 24 months of at least 20 mm on a 100 mm VAS from the baseline level. Data regarding pain improvement will be provided for all pain components (*i.e.*, low back, right leg and left leg). The

above improvement criterion of 20/100 mm refers to the dominant pain component for each patient. For example: if the preoperative VAS (pain) for a given patient was 90 (low back), 60 (right leg), and 40 (left leg), improvement of at least 20 mm will be required for the back pain component. Improvement in both legs, though, will be also reported.

- Individual patient clinically meaningful improvement with respect to ***functionality*** is defined as postoperative improvement at 24 months of at least 15 points on the ODI graded on a 100-point scale as compared to baseline assessment.

It is noted, that the indicated improvement values in pain and function are regarded clinically meaningful and were used in other, IDE studies for similar devices.

Average improvement and standard deviation for VAS (pain) and ODI, as well as the proportion of patients that met the success criterion for VAS and ODI, will be reported. The VAS and ODI results obtained in the study shall be also compared to VAS and ODI results reported in the literature (as summarized in **Section 5.2.1**).

5.10.3 SAFETY EVALUATION

The safety evaluation will be based on the reported complications and adverse events (AEs), including subsequent surgical interventions and neurological status. Complications/Aes shall be evaluated at each follow-up session, as well as throughout the study.

1. <u>Complications/Adverse Events</u>

All the reported complications/adverse events, whether device-related or not, including "anticipated" complications, will be recorded.

Refer to **Section 5.14.4.1** for adverse event definitions.

2. Subsequent Surgical Intervention

Information regarding subsequent interventions will include category of procedure, as defined below, the reason for the procedure and whether or not the subsequent procedure constitutes a study failure.

Subsequent surgical intervention will be categorized as a revision, removal, re-operation, or supplemental fixation at the affected level/s, as defined hereinafter.

Revision – a second 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.

Removal – a procedure where *all* of the original system configuration are removed with or without replacement.

Reoperation – any surgical procedure at the involved level/s that is not removal, modification, or addition of any components to the system (*e.g.*, irrigation and debridement).

Supplemental Fixation – a procedure in which additional instrumentation not under study in the Protocol is implanted.

Subsequent interventions in spinal studies include epidural injections, the implantation of spinal stimulators, and rhizotomies.

3. Neurological Status

A neurological examination will be performed preoperatively and at discharge, and at all postoperatively visits, to assess neurological status. The evaluation of neurological status will include motor, sensory, reflex, straight leg raising, and tenderness assessments, as hereby described. Each component shall be assessed separately on each anatomical side (left, right). The following paragraphs describe the five neurological examinations.

The **motor evaluation** measures the muscle strength in major muscle groups (Gluteus Maximus (hip extension); Iliopsoa (hip flexion); Quadriceps (knee extension); Hamstrings (knee flexion); Anterior Tibial Group (ankle dorsiflexion); Extensor Hallucis Longus (great toe extension); Posterior Tibial (ankle plantar flexion/eversion); and Flexor Halluces (great toe flection)). Muscle strength is evaluated on a 6-point scale ranging from 0 to 5 according to the following key

describing the ability of the patient to move the lower extremities against resistance provided by the examiner:

- 0 – no movement;
- 1- muscle contraction;
- 2 – lateral movement;
- 3 – against gravity;
- 4 – against moderate resistance;
- 5 – against full resistance.

Light-touch will test **sensation** for all lumbar and sacral dermatomes in comparison to the contralateral site. The sensation shall be graded as equivalent (normal), impaired, absent, as compared to the contralateral side.

Reflexes (Patella and Achilles) are evaluated according to Bate's Reflex Scale (a 5-point scale ranging from 0 to 4) as follows:

- 0 – no reflex;
- 1 – somewhat diminished, low normal;
- 2 – average, normal reflex;
- 3 – brisker than average;
- 4 – very brisk, hyperactive.

Straight leg raising is assessed by measurement of the degree of movement required to reproduce symptoms. A positive test is considered when the patient reports worsening of pain between 30 and 70 degrees of hip passive flexion while knee is extended.

Tenderness will be evaluated by palpation of the lower spine area – lumbar paraspinal region, lumber spinous process, sacroiliac joint, and sciatic notch. Tenderness shall be graded as negative or positive (*i.e.*, palpation provokes painful sensation).

Patient Success –

Individual patient success with respect to ***safety*** is defined as:

- No worsening in neurological status (motor, sensory, reflex, straight leg raising, and tenderness assessments) and no new permanent neurological deficits present for at least 2 successive visits at or beyond 6 months (out to 24 months);
- Absence of device-related serious adverse events through 24 months;
- Absence of subsequent surgical interventions at the index level through 24 months.

5.11 EVALUATION OF SECONDARY OUTCOME MEASURES

A. Patient's Overall Well-Being and Satisfaction

Subject's overall well-being and satisfaction will be assessed using dedicated questionnaires.

SF-12 (Subject Overall Well-Being):

Subject's overall well-being (quality of life) will be assessed using the 12-Item Short Form Health Survey (SF-12), which is a multipurpose short-form quality of life instrument with 12 questions selected from the SF-36 Health Survey. SF-12 questionnaire is designed to measure general health status from the patient's point of view. Results are expressed in terms of two meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS Score is a composite of the Physical Functioning, Role Functioning, Bodily Pain and General Health Scales within the SF-12 instrument. The MCS is a composite of the Vitality, Social Functioning, Role-Emotional and Mental Health Scales within the SF-12 instrument. The SF-12 is a normative based instrument. PCS and MCS are computed using the rating on 12 questions from 0 to 100, where a 0 score indicates the lowest level of health and 100 indicates the highest level.

The SF-12 questionnaire will be administered preoperatively as well as at each postoperative visit, starting at 6 weeks visit.

VAS (Patient Satisfaction):

Patient satisfaction will be assessed using a 100 mm VAS, completed by the patient. Satisfaction scores shall be obtained from patient responses, and shall be expressed in millimeters (mm). The anchor points are "Completely Not Satisfied" (0 mm) and "Completely Satisfied" (100 mm). Patients shall be instructed to draw a single line across the scale at the point that best described their level of satisfaction.

VAS questionnaire for satisfaction will be administered at each postoperative visit, starting at 6 weeks visit.

B. Donor Site Pain

The assessment of pain at the donor site (iliac crest) shall be performed using scores determined from measurements of responses to pain question, provided on a 100 mm VAS. The anchor points are "No Pain" (0 mm) and "Severe Pain" (100 mm). Patients for which bone graft was harvested from their iliac bone will be instructed to draw a single line across the scale at the point that best described their level of pain at the donor site.

VAS questionnaire for donor site pain will be administered at each postoperative visit, starting at 6 weeks visit.

C. Operative Information

Parameters related to the surgery, such as blood loss and operation time will be also evaluated for all patients participating in the study.

The volume of ***blood loss*** during operation will be recorded for each patient, and average blood loss and standard deviation will be reported in cubic centimeter (cc).

Operation time (skin-to-skin) will be recorded for each patient, and average operation time and standard deviation will be reported in minutes.

5.12 STUDY SUCCESS CRITERIA

The results of the study at 12 months and 24 months postoperatively for all participating subjects will be evaluated, with reference to the reported results from the

literature, as summarized in **Section 5.2.1**. In addition, assessment of success rate will be conducted at each time point, as applicable.

In addition to evaluating individual patient success as the primary composite endpoint, each element of the composite will be evaluated individually as secondary endpoints, as described below.

Fusion – Success for the fusion outcome measure will be defined as two year fusion rate comparable to the two and one year fusion rates presented in the literature. The pooled results of the Company literature research (for patients with DDD treated with pedicle screws with PLIF/ALIF/TLIF and/or PLF), as presented in **Section 5.2.1**, demonstrated at 12 and 24 months postoperatively fusion rates in the different studies ranging from 77% to 97%.

As discussed in **Section 5.2.1.A**, the weighted average for the fusion rate of the ten articles is 87.79%. Based on the literature, we believe our fusion rate will be 88%.

The assumed fusion rate of 88% has a 95% confidence interval of ±6.4% for 100 patients. Notably, the lower bound of this confidence interval, 81.6%, is within the range of the fusion rates reported in the selected literature.

Safety – Success with regard to safety outcome measure is defined as no worsening in neurological status (motor, sensory, reflex, straight leg raising, and tenderness assessments) and no new permanent neurological deficits (present for at least 2 successive visits at or beyond 6 months), absence of device-related serious adverse events, and absence subsequent surgical interventions at the index level, through 24 months, comparable to neurological deficit, device-related serious adverse events, and subsequent surgical interventions rates presented in the literature.

Based on the literature review in FDA's Executive Summary, the rate of these events in the literature control is 13.5%.

Therefore, the Company estimates that the adverse event rate for these events will be 13.5%. With a sample size of 100 patients, this adverse event rate has a 95% confidence interval of ±6.7%.

As indicated above, it is believed that at the time all subjects from the IDE study complete one year follow-up, supporting safety data for 24 months will be available for about 45 patients from the ongoing, OUS study.

Pain - Individual patient, clinically meaningful, improvement with respect to pain is defined as postoperative improvement at 24 months of at least 20 mm on a 100 mm VAS from the baseline level.
Value of 73% of patients with ≥20 mm improvement. This value is selected as it is consistent with the performance of the Silhouette Spinal Fixation System reported in P070031.

Function - Individual patient, clinically meaningful, improvement with respect to function is defined as postoperative improvement at 24 months of at least 15 points on the ODI graded on a 100-point scale as compared to baseline assessment.
Value of 55% of patients with ≥15 points improvement. This value is selected as it is consistent with the performance of the control group reported in P050010.

Individual Patient Success (Overall Success)

Individual patient success (*i.e.*, overall success) will be determined at 24 months and is defined as a composite primary endpoint. An individual subject will considered a success if all of the following criteria are met:

- Presence of continuous bridging bone between the involved motion segment at 24 months, *i.e.*:
  - Presence of interbody bridging bone and absence of radiolucency > 50%; OR
  - Presence of left posterolateral bridging bone; OR
  - Presence of left posterolateral bridging bone.
- No motion on flexion/extension films at 24 months (success is defined as angular motion < 3º and translational motion < 3 mm);
- Improvement of at least 20 mm on a 100 mm VAS from baseline level at 24 months;
- Improvement of at least 15 points on the ODI graded on a 100 point scale at 24 months as compared to baseline;
- No worsening in neurological status (motor, sensory, reflex, straight leg raising, and tenderness assessments) and no new permanent neurological

deficits present for at least 2 successive visits at or beyond 6 months (out to 24 months);

- Absence of device-related serious adverse events through 24 months;
- Absence of subsequent surgical interventions at the index level through 24 months.

The study will be considered a success if the overall success rate for the CarboClear Device is 41%. This value is selected as it is consistent with the performance of the control groups reported in P050010 and P070031.

5.13 STATISTICAL ANALYSIS

5.13.1 SAMPLE SIZE JUSTIFICATION

Fifty five (55) patients will participate in the IDE study. However, the statistical analysis will be conducted for a total sample size of 100 patients as the Company is adding data from ongoing OUS sites to data collected according to this IDE. FDA confirmed that the proposed IDE sample size, in addition to the ongoing OUS data, would be sufficient. It is emphasized, that prospectively enrolled patients at OUS sites will participate in the study presented in this IDE (*i.e.*, will be part of the 55 patients of the IDE study), and will follow the same protocol that representing homogenous cohort of DDD patients with up to Grade I spondylolisthesis and no greater than mild stenosis. Only currently enrolled patients in the ongoing OUS sites that are adequately per IDE protocol (about 45 patients) will be considered in the statistical analysis. Adequacy for OUS study patients being included in the statistical analysis will be based, mainly, on patient meeting the eligibility criteria (inclusion/exclusion) for the IDE study, *i.e.*, DDD patients, with up to Grade I spondylolisthesis and/or with up to mild stenosis (the ongoing OUS study was approved for more heterogenic population). Other parameters, as detailed below, are very similar when comparing the ongoing OUS study and the study suggested in this IDE: The same system and surgical technique are used in both studies. The IDE study includes the use of an interbody fusion device while the OUS study does not. Thus, the data from the OUS study may be regarded as worst case in terms of fusion rates as only posterolateral fusion was made and interbody fusion device was not used. Patient population is

considered similar in both studies (demographically, as well as indications wise, as non-DDD patients will not be included in the statistics for the IDE study). The endpoints for the IDE study are also evaluated in the ongoing OUS study, using the same assessment tools: fusion (radiographs), safety, pain (VAS), function (ODI), and patient well-being (SF-12). Follow-up time points are similar in the ongoing OUS study (4 weeks, 3 months, 6 months, 12 months and 24 months) and the suggested IDE study (6 weeks, 3 months, 6 months, 12 months, and 24 months, and then annually, until the last patient completed 2-year follow-up).
As it is estimated that data for about 45 patients will be available from the ongoing OUS study, the total sample size is effectively 100 patients.

It is noted, that the suggested investigation is a confirmatory study, aimed at supporting the safety and effectiveness of the CarboClear System. As indicated before, comprehensive pre-clinical testing was conducted for the system, with good results, substantially equivalent to the results of cleared predicate devices (metal, rigid, pedicle screw systems). In addition, interim results from the ongoing, OUS study with the CarboClear System support the safety and effectiveness of the system for DDD patients (as summarized in the Investigator Brochure, the OUS trial enrolls DDD patients, as well non-DDD patients/patient with DDD and other pathologies. The latter may be regarded as worst case with respect to pedicle screw instrumentation and fusion in comparison to DDD patients).
Based on the above, and taking into account the selection of narrow indication for the study that results in homogenous population, the number of 55 subjects for this confirmatory study is thought to be sufficient (with statistical analysis of 100 patients).

5.13.2 POOLABILITY OF DATA

All data obtained from up to 8 sites participating in this study will be pooled into a single database for which data analysis will be performed.
Poolability is considered to be appropriate as all sites will use the same study Protocol and Appendices (such as Case Report Forms). Also, all investigational teams will

receive the same training by the Sponsor representative. The appropriateness of pooling data from multiple centers is necessarily enhanced by training all participating centers to follow the same protocol, with, among other things, clearly defined inclusion and exclusion criteria for study participation. Periodic monitoring visits shall be conducted to verify full understanding and fulfillment of the procedure at all sites. In addition, performance and evaluation of X-Rays images will be performed using the same means and definitions, according to written radiographic protocol, by the same independent reviewers. Likewise, independent reviewers (clinical events committee) will assess all adverse events to determine the severity of the events and their relationship to the procedure and investigational device (please refer to **Section 5.14.4**). Thus, this multi-center study includes standardization of subject enrollment, data collection and evaluation, and adverse event reporting and evaluation, with all sites following the requirements of the same Protocol.

Prior to pooling the data, the demographic information items will be reviewed to verify that their average values for all sites are within one standard deviation. Furthermore, the Company will perform poolability analyses of baseline characteristics and cage type in order to confirm the homogeneity of the entire patient population.

In particular, before combining the US and OUS data (*e.g.*, patients from US and patients from OUS in the proposed study; as well as patients from the proposed IDE study and patients from the ongoing OUS study) the baseline demographics and prognostic characteristics between the groups will be compared to evaluate the poolability of the US and OUS data. The characteristics to be compared include:

- Age
- Gender
- Pre-operative VAS
- Pre-operative ODI
- Diagnosis (DDD, Degenerative Spondylolisthesis ≤ Grade I, Spinal Stenosis < 40%, or other)
- Previous spinal surgical treatment (yes/no)
- Type of interbody fusion device used (for subjects participating in the IDE study)

These characteristics will be compared using a t-test or a Wilcoxon rank sum test for continuous variables and a Chi-square test or a Fisher's exact test for categorical variables, as appropriate. If the OUS data is similar to the US data then the data will be pooled and analyzed as a single group. If the US and OUS data are dissimilar, then the combining of the two datasets may need to be reevaluated. The reasons for dissimilarity will be investigated and the effect of investigational treatment in the presence of the disparate results will be discussed. In addition, primary analysis results stratified by US and OUS sites will be presented.

With regards to the ongoing OUS study – as described in the above **Section 5.13.1**, poolability of data for the statistical analysis is deemed eligible.

5.13.3 ANALYSIS POPULATIONS

Intent-to-Treat ("ITT"): All patients treated with the device.
Per-Protocol ("PP"): All patients who did not have a major protocol violation and who completed all study visits.
The primary analysis will be based upon the ITT population. Additional analyses using the PP population will also be presented in the final report.

5.13.4 STATISTICAL ANALYSIS OF DATA

In general, the statistics for numerical variables shall be presented as mean ± standard deviation, median, minimum and maximum values (range), and sample size (continuous data). Categorical data will be presented as counts (numbers) and percentage of the total (rate). In addition, 95% confidence intervals will be presented for the fusion and adverse events rates. Furthermore, subgroup summary statistics will be calculated where necessary.
Where adequate, comparison between subgroups (*e.g.*, with/without mild stenosis; with/without prior discectomy) shall be presented with differences (*e.g.*, P-values). It should be noted that comparisons between subgroups are supportive analyses; these p-values will not be adjusted for multiplicity.

Adverse events (AE) data will be listed individually and summarized. Overall AE results will be presented both on a per-subject basis and per-event basis (*i.e.*, total number of subjects with each event and total number of events reported).

Results of AE seriousness and device-relatedness will be presented as well.

The report of AEs based on specific type of event will be according to the following AE terms, listed in the table below, and in accordance with FDA list of risks applicable for pedicle screw spinal systems (FDA's Executive Summary, Table 11).

ADEVERSE EVENTS
Implant Malposition
Implant Loosening
Device Breakage
Construct Disassembly
Bone Fracture
Graft Settling/Displacement
Loss of Correction
Pseudoarthrosis
Bleeding/Vascular Injury
Neurologic Injury
Back/Leg Pain (Radiculopathy)
Dural Tear/CSF Leak
Wound problems
Infection/Sepsis
Skin Irritation
Cardiac
Respiratory
Gastrointestinal
Reoperation/Revision
Death

In addition, as per the FDA recommendation, the adverse events will be further analyzed according to the Adverse Events table provided in **Section 5.14.4.2**.

Patients who withdraw from the study (following implantation of the investigational device), are lost to follow-up, or for whom data is missing, will be analyzed individually based on the information already available for the patient. In general, if sufficient data will be available for the patient based on previously gathered

information (*e.g.*, at previous follow-up sessions) or if, in cases where fusion occurs prior to withdrawal and no adverse events have been observed, the patient may be regarded as a success.

5.14 SUMMARY OF RISK ANALYSIS

5.14.1 POSSIBLE HAZARDS

The risks and possible adverse events associated with the use of CarboClear Pedicle Screw System and the discussed procedure are expected to be similar to- and are not expected to be at a higher rate than those related to other pedicle screw-based devices and procedures available on the market.

Those risks/possible adverse events include:

(a) risks associated with undergoing surgery;
(b) risks associated with spine surgery;
(c) risks associated with fusion surgery of the lumbar spine; and
(d) risks associated with the use of the CarboClear Pedicle Screw System.

The individual risks associated with each of the above groups are provided below.

Risks Associated with Undergoing Surgery

- Infection/Sepsis.
- Development of respiratory problems, *e.g*. atelectasis, bronchitis, pneumonia, *etc*.
- Haemorrhage of blood vessels and/or haematomas occlusion, seroma, edema, hypertension, embolism, stroke, excessive bleeding, phlebitis, wound necrosis, wound dehiscence, damage to blood vessels, or other types of cardiovascular system compromise.
- Deep venous thrombosis, thrombophlebitis and/or pulmonary embolus.
- Damage to lymphatic vessels and/or lymphatic fluid exudation.
- Reactions to the drugs or anesthetic agent used during and after surgery.
- Ileus, gastritis, bowel obstruction or loss of bowel control or other types of gastrointestinal system compromise.

- Reactions to transfused blood.
- Incisional pain.
- Change in mental status.
- Death.

Risks Associated with Spine Surgery

- Loss of neurological function (*e.g.*, sensory or motor), including paralysis (complete or incomplete), appearance of radiculopathy, dysesthesias, hyperesthesia, anesthesia, paresthesia, and/or the development or continuation of pain, numbness, neuroma, spasms, sensory loss, tingling sensation, and/or visual deficits.
- Cauda equina syndrome, neuropathy, neurological deficits (transient or permanent), paraplegia, paraparesis, reflex deficits, irritation, arachnoiditis, and/or muscle loss.
- Dural tear experienced during surgery could result in the need for further surgery for dural repair, a chronic cerebral spinal fluid leakage or fistula, and possible meningitis.
- Herniated nucleus pulposus, disc disruption or degenerative changes or instability at, above, or below the level of surgery.
- Loss of or decrease in spinal mobility or function.
- Loss of proper spinal curvature, correction, height and/or reduction.
- Bone fracture or bone loss or decrease in bone density, possibly caused by stresses shielding at, above, or below the level of surgery.
- Tissue or nerve damage caused by improper positioning and placement of implants or instruments.
- Vascular damage due to surgical trauma or presence of the device could result in catastrophic or fatal bleeding. Malpositioned implants adjacent to large arteries or veins could erode these vessels and cause catastrophic bleeding in the late postoperative period.
- Bursitis.

- Scar formation possibly causing neurological compromise or compression around nerves and/or pain.
- Inability to resume activities of normal daily living.
- Reproductive system compromise, including sterility, retrograde ejaculation, and sexual dysfunction.
- Urinary retention or loss of bladder control or other types of urological system compromise.
- Risk of radiation exposure preoperatively, during surgery and following operation, during follow-up sessions (*e.g.*, fluoroscopy, X-Rays, and optionally CT scans).

  The series of radiographs required for this study are similar to the standard of care for patients with similar traditional surgical procedures. The risk of any side effects from this low level of exposure is very small. It is estimated that the total millirems will be less than 200 millirems per visit (for a 4 view x-ray) or no more than 1300 millirems for the duration of this study. This exposure can be compared to the allowable annual radiation dose for nuclear medicine/radiation oncology workers of 1800 millirems per year.[23] The consequences of this radiation are small, but can include developing cancer later in life from the radiation.[24] Radiation exposure associated with computed tomography (CT) scans of the lumbar spine is higher, and may approach 6 milliSieverts, or the equivalent of approximately 730 days of natural background radiation (at 3 mSv/year). The consequences of CT scans are small, but can include developing cancer later in life, and potential reactions to contrast agent.[24]

[23]http://www.fda.gov/RadiationEmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicaiX-Rays/ucm175028.htm
[24]http://www.fda.gov/RadiationEmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicaiX-Rays/ucm115317.htm

Risks Associated with Fusion Surgery of The Lumbar Spine

- Graft settling/displacement.
- Non-union (or pseudarthrosis), delayed union or mal-union.
- Donor site pain.
- Risks pertaining to the use of allograft (if applicable), including infection, fever, incomplete bone ingrowth, delayed fusion or non-union, hypercalcemia or transient hypercalcemia, disease transmission and undesirable immune response.

Risks Associated with The Use of The CarboClear Pedicle Screw System.

- Disassembly, loosening, bending or fracture of any or all of the implant components.
- Implant migration.
- Foreign body (allergic) reaction to the implants, debris, including possible staining, autoimmune disease, tumor formation and/or scarring.
- Pressure on the surrounding tissues or organs.
- Pressure on the skin from component parts in patients with inadequate tissue coverage over the implant, possibly causing skin penetration, irritation, fibrosis, neurosis, and/or pain.

Additional surgical intervention may be necessary to correct some of the possible adverse events. Surgical intervention may be a revision surgery, a removal procedure, re-operation, or supplemental fixation.

This list of potential risks is presented, in the same manner, in the patient Informed Consent document, in the Case Report Forms, and in the IFU (Package Insert) for the system.

5.14.2 RISK REDUCTION MEASURES

Risk management activities are carried following the guidelines provided in ISO 14971 Standard (Medical Devices – Application of Risk Management to Medical

Devices). The analysis of risks was performed using the Failure Mode and Effect Analysis (FMEA) in its extended version (FMECA), in accordance ISO 14971 and IEC 812 (Failure Mode and Effects Analysis).

CarboFix activities, from initial design stages, are aimed at minimizing as possible faults, malfunctions, incidents, *etc*., related to the device. In order to reduce the risk of patient (or user) harm or a fault/damage to the device during its usage, the following measures are taken:

a. Design activities according to written design control procedures;
b. Risk management activities, including risk analysis;
c. Biocompatibility evaluation;
d. Conducting pre-clinical, comprehensive bench testing and cadaveric study;
e. Manufacturing according to quality system requirements (*e.g*., production according to approved specifications, drawings and instructions; performing quality controls to incoming raw material, following production stages, and to finished devices; *etc*.);
f. Providing a clear Instructions for Use document (IFU) and Surgical Technique. Among other things, these documents include description of the system and its components (including figures), indications for use and contraindications, possible adverse events, warnings and precautions, instructions regarding system preparation, surgical procedure description, information regarding the compatibility of the product with other devices, and information regarding product packaging and sterilization.
g. Conducting additional validations and verifications, as applicable, such as sterilization validation.

The following paragraphs specifically address the risks indicated above, and the measures by which those potential risks are minimized.

A. Risks Associated with Undergoing Surgery

General operative-related complications (such as infection/sepsis, bleeding/vascular injury, respiratory and cardiac complications, anesthesia, wound complications and

pain, *etc*., as listed above) are expected to be similar in nature and not in higher rates compared to those seen with other pedicle screw systems, as the surgical procedure is the same.

As the implantation procedure is similar to that used for other pedicle screw system implantation, using similar surgical instruments, and as cleared interbody fusion device is used, no additional/special hazards are expected to rise from the operation procedure itself.

It is noted, that the implantation procedure and the performance of the surgical instruments were also evaluated during cadaveric study.

In addition, the CarboClear System is currently under multi-center study conducted out-of-the-US. So far, 47 patients were already treated with the system, with a follow-up duration of up to over one year (40 of which had diagnosis that complies with the indications proposed in the IDE (*i.e*., DDD patients with up to Grade I spondylolisthesis). The following adverse event, which may be categorized as related to undergoing surgery, was reported in the said study:

In one patient, fever was developed following uneventful operation and discharge (5 days following surgery). CT images revealed well-positioned implants with no root irritation. The surgical wound was healed, with no infection. Blood cultures were negative. The patient was hospitalized and treated with intra-venous antibiotics for three days, and was then discharge from the hospital with additional 2 weeks of antibiotics. Fever was probably related to pneumonia. The patient healed and is doing well.

B. Risks Associated with Spine Surgery

Complications associated with spine surgery (as listed above) are expected to be similar in nature and not in higher rates compared to those seen with other pedicle screw systems, as the implant components design and dimensions, and the surgical procedure for their implantation (as well as the use of the cleared intervertebral fusion device), are similar.

As the implantation procedure is similar to that used for other pedicle screw system implantation, using similar surgical instruments, no additional/special hazards are

expected to rise from the spinal procedure in comparison to other, similar spinal surgeries.

It is noted, that the implantation procedure and the performance of the surgical instruments were evaluated during cadaveric study.

Regarding the risk of radiation exposure, no additional risk of radiation exposure is expected prior to-, during the implantation of the CarboClear device as well as during follow-up sessions, compared to radiation exposure associated with similar spinal implants that are being investigated in clinical studies. The risk of radiation exposure during implantation procedure is also expected to be the same as that for cleared pedicle screw systems. It is expected, though, that subjects participating in a clinical study for spinal implants may undergo additional imaging at follow-up sessions and thus the risk of radiation exposure may be slightly higher for this population compared to patients undergoing spinal surgery with a cleared device.

In addition, data from the on-going OUS clinical investigation (for the 40 patients that comply with the indications for the proposed IDE study) supports the similarity between the CarboClear spinal surgery parameters with those of other, similar devices:

Operation Time - Average total operation time recorded during the said 40 surgeries with the CarboClear System was 115.1 minutes (±23.4 minutes), ranging from 72 to 185 minutes. Operation time reported for the surgeries carried to date is similar to that reported by others for this type of surgeries (for example, Kim *et al*. [25] report average operation time of 196 minutes, and Dimar *et al*. [1] – 174 minutes).

Blood Loss - Average blood loss recorded during the 40 surgeries was 379.4 cc (±125.6 cc), ranging from 200 cc to 600 cc. Blood loss reported for the surgeries carried to date is similar to that reported by others for this type of surgeries (for example, Dimar *et al*. [26] report average blood loss of 448.6 mL, and Kang *at al*. [27] - 512.5 mL).

[25] Kim KK, Lee SH, Lee YH, Bae SC, Suk KS, Clinical Outcomes of 3 Fusion Methods through the Posterior Approach in the Lumbar Spine. Spine 2006; 31 (12): 1351 – 1357.

[26] Dimar JR, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Two-year fusion and clinical outcomes in 224 patients treated with a single-level instrumented posterolateral fusion with iliac crest bone graft. *The Spine Journal* 2009;9:880–885.

Fluoroscopy Time - Average fluoroscopy time recorded during the 40 surgeries was 38.7 seconds (±18.9 seconds), ranging between 20 and 100 seconds. Fluoroscopy time reported for the surgeries carried to date is similar to that reported by others for this type of surgeries (for example, Jones *et al*. [28] report fluoroscopy time of 1.4 minutes (*i.e*., 84 seconds) per case or 0.33 minutes per screw, in a series of 140 patients who underwent pedicle screw fixation; Mulconrey [29] reported mean fluoroscopic time of 1.74 minutes (104.4 seconds) with lumbar spine instrumentation).

The on-going clinical investigation with the CarboClear device also supports the proper visualization of implant components, either during operation or at follow-up period. This minimizes the risk of pedicle screws malpositing, and subsequent adverse events such as nerve tissue injury and possible additional surgical intervention. Pre-clinical evaluation of implant components was conducted during cadaveric study, using three imaging modalities (X-Rays, CT and MRI).

In addition, the following adverse event, that may be categorized as related to spinal surgery, was reported in the OUS study (for the 40 DDD patients):

About 1 week post-operation the patient complained of radicular pain, with no motor deficiency and no fever. CT demonstrated mild compression and edema, with no nerve root irritation. The implants seemed well positioned and intact. The patient was re-operated (exploratory surgery), revealing mild compression at the surgery site. The instruments were well positioned and stable. During this surgery additional decompression at one level above the surgery was performed. All symptoms resolved after second operation, with improvement in pain and functionality parameters at 3 months follow-up as compared to pre-operation data.

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[27] Kang J, Howard A, Hilibrand A, Yoon ST, Kavanagh E, Boden S. Grafton and Local Bone Have Comparable Outcomes to Iliac Crest Bone in Instrumented Single-Level Lumbar Fusions. *Spine* 2012;37(12):1083–1091.

[28] Jones DP, Robertson PA, Lunt B, Jackson SA, Radiation exposure during fluoroscopically assisted pedicle screw insertion in the lumbar spine. *Spine* 2000; 25 (12): 1538-41.

[29] Mulconrey DS, Fluoroscopic Radiation Exposure in Spinal Surgery: In Vivo Evaluation for Operating Room Personnel. *J Spinal Disord Tech.* 2013 Nov 7 [Epub ahead of print].

The event was categorized as not related to the device, and possibly related to the procedure.

C. Risks Associated with Fusion Surgery of The Lumbar Spine

Complications associated with lumbar fusion include, on top of spinal surgery risks indicated above, graft settling/displacement, non-union (pseudarthrosis), delayed union or mal-union, and donor site pain. Additional risks may be associated with the use of allograft (if used), as listed above. It is noted, that the CarboClear device may be implanted with autogenous and/or allogenic bone graft.

Those complications are expected to be similar in nature and not in higher rates compared to those seen with other pedicle screw systems, as the surgical procedure and instruments used for fusion, as well as the cleared interbody fusion device and bone graft materials, are similar.

Data from the on-going OUS clinical investigation accumulated so far (for the 40 patients that comply with the indications for the proposed IDE study) support the safety and effectiveness of the CarboClear System and indicate the following fusion rates:

- At 6 months (1 level): 25/26 patients (96.2%);
- At 12 months (1 level): 3/3 patients (100%);
- At 6 months (2 levels): 1/1 (100%).

It is noted, that comparative bench testing conducted for the system (as detailed in the Investigator Brochure) supports the similar performance of the system and cleared, metal, pedicle screw systems in terms of both test results and failure modes. In particular, with respect to the ability of the CarboClear rods to provide for adequate stiffness to support fusion - long-term stability and stiffness of the CFR-PEEK rods were successfully evaluated in static and dynamic tests conducted for the entire implant construct, as well as in 4-point bending test and creep test conducted for the rods.

As it is postulated, based on all the above, that the risk of non/delayed/mal fusion would not be at a higher rate than that seen for other cleared, rigid, pedicle screw systems, it is expected that the risk of re-operation due to those risks will also be at similar rate as the rate reported for other rigid pedicle screw systems.

D. Risks Associated with The Use of The CarboFix Pedicle Screw System

In general, risks related to the use of the device are mitigated by the following measures:

- Implant components are similar in design and dimensions to those of other, cleared, rigid pedicle screw systems. As with other pedicle screw systems, the CarboClear components allow the surgeon to build an implant construct to fit the patient's anatomical and physiological requirements (*e.g.*, the screws and rods are provided in various dimensions, the pedicle screws comprise a polyaxial head, and the rods are provided either straight or curved, all of which provide for an implant construct that meets the anatomical needs of the patient);
- The surgical instruments of the system and the surgical procedure are similar to those used with other, cleared, pedicle screw systems;
- Extensive biomechanical study was performed, as summarized below and detailed in the Investigator Brochure, with results and failure modes equivalent to those of the predicate devices;
- Supportive clinical data are available from OUS clinical trial, as summarized in the Investigator Brochure;
- Training of the study investigators;
- Providing IFU (Package Insert) and Surgical Technique documents, as detailed below;
- The use of the system is limited to only experienced spinal surgeons with specific training in the use of this system;
- The system is designed, processed, assembled, tested, and packaged according to the Company approved procedures. Wherever required, processes are being

verified and validated according to the Company approved procedures and international standards.

The specific risks are detailed below, with the manner of their mitigation.

Implant Mechanical Failure - Disassembly, Loosening, Bending, Fracture or Migration

The CarboClear device was tested in a comprehensive *in-vitro* study and a cadaveric study, to validate its design and to assess its performance (*e.g.*, bone purchase and function) and integrity (of the components and construct). Pre-clinical testing included the following tests:

- Static axial compression bending test (ASTM F 1717)
- Static torsion test (ASTM F 1717)
- Fatigue axial compression bending test (ASTM F 1717)
- Fatigue lateral bending-axial rotation test
- Wear debris evaluation following fatigue testing (ASTM F 1877)
- Axial gripping capacity test (ASTM F 1798)
- Flexion-extension moment test (ASTM F 1798)
- Axial torque gripping capacity test (ASTM F 1798)
- Pull-out test (ASTM F 2193, ASTM F 543)
- Rod 4-point bend test (ASTM F 2193)
- Titanium shell shear test (ASTM F 1044)
- Rod creep test
- Cadaveric study

Where applicable, tests were conducted in a comparative manner, to FDA-cleared predicate devices (rigid pedicle screw systems). Bench testing demonstrated substantial equivalent results and same failure modes. Please refer to the Investigator Brochure, for detailed description of the said tests.

Various tests, and in particular fatigue tests, were performed to verify no failure of the implant (*e.g.*, breakage, deformation, or disassembly) will occur prior to fusion. In fatigue axial compression bending test, the device construct successfully completed five million cycles under a load of 300 N, corresponding to 83% of its ultimate load. Lateral bending-axial rotation fatigue tests, conducted to further support the system

mechanical properties and the equivalency to rigid, metal, pedicle screw systems, demonstrated the device completed $5x10^6$ cycles at high moment of at least 8.5 Nm with no failure.
Macroscopic and microscopic examination of the devices following the said fatigue tests indicated no plastic deformation of the rods. No scarring formation was detected. Wear debris analysis following fatigue tests indicated that only small amount of CFR-PEEK debris was generated following successful completion of $5x10^6$ fatigue cycles at relatively high loads and/or moments.

Regarding ***loosening/disconnection*** of implant components - the CarboClear device is designed to prevent movement between its components, immediately upon locking. The rod is secured to the screw using a taper locking element, that accommodates the rod and is introduced within the screw tulip. Loosening/disconnection of components was assessed in several tests following the guidelines set in ASTM F 1798, which were designed to evaluate the interconnection mechanism of the device. Additional tests which evaluated the entire CarboClear construct, including fatigue tests, also demonstrated that the locking mechanism of the system is effective and comparative to cleared rigid pedicle screw systems.

It is noted, that the screw is provided with a thin titanium shell, thus bone-implant interface is similar to that of other, cleared, pedicle screws.
Shear test was successfully conducted to verify the integrity and connection of the titanium shell to the CFR-PEEK screw.
As for ***implant migration*** - pullout tests performed to the CarboClear pedicle screws demonstrated that their pullout strength is similar to that of cleared predicate devices.

Nonunion, Delayed Union or Malunion
Long-term stability and stiffness of the CFR-PEEK rods (adequate stiffness to achieve fusion) were evaluated in static and dynamic tests conducted for the entire construct (*i.e.*, four screws and two rods), as well as in 4-point bending test and creep test conducted for the rods.

The results of the said tests indicated excellent fatigue properties and similar stiffness as compared to titanium pedicle screw constructs and titanium rods.

The results obtained for the creep test, following more than five weeks under a high continuous load of 450 N and at a temperature of 70° C (conditions which simulate a year at 37° C and extreme loading), demonstrate no plastic deformation to any of the rods and high creep resistance.

Implant Malposition

Similarly to implantation of other pedicle screw systems, the surgical procedure is monitored radiographically, to verify, among other things, proper location of the screws and final construct positioning. Radiographic evaluation is also performed post-operatively.

The implant components of the CarboClear System are made of radiolucent material - CFR-PEEK, with metal radiopaque markers intended to enable implant visualization under imagine. Especially, the threaded portion of the pedicle screws is encased within a thin layer titanium shell. The titanium shell mark the borders of the screw thread and distal tip, thus facilitating proper insertion of the screws under fluroscopy visualization, as well as monitoring their location (*e.g.*, relative to nerve tissue) and integrity post-operatively. The other implant components comprise a tantalum marker.

In accordance with FDA recommendation, the Company has conducted cadaveric study in a human spine, demonstrating the visualization of the CarboClear implants using the following imaging modalities: MRI, CT and X-rays.

It is emphasized, that due to the relative small metal content, the screws do not interfere with CT and MRI imaging while allowing screw visualization under X-rays.

In addition, the implantation procedure and the performance of the surgical instruments were also evaluated during cadaveric study.

Foreign Body Reaction to the Implant

The implant components are made of CFR-PEEK (Ultra Reinforced-PEEK-OPTIMA® (Endolign), by Invibio), with radiopaque markers.

The screw threaded portion is encased within a thin shell made of pure titanium (conforming to ASTM F 67). The other CFR-PEEK components include a tantalum (per ASTM F 560) marker, embedded within the CFR-PEEK during molding process. The said materials are acceptable for use in long-term implants and exist in other, cleared spinal implants (including their combination).

In addition, the different manufacturing processes (*e.g.*, compression molding) do not include the use of any additive, releasing agent, *etc*. For a detailed biocompatibility evaluation, please refer to the Investigator Brochure.

As indicated before, evaluation of wear debris generation was conducted following successful completion of five million fatigue cycles at relatively high loads and moments, as well as following device failure. Analysis of collected material demonstrated that only a small amount of CFR-PEEK debris was generated. The description of the wear debris tests is provided in the Investigator Brochure.

Infection (Non-Sterile Device)

Regarding the risk of infection due to non-sterile device - the implants will be supplied sterile (by moist-heat steam) and labeled for single use. The multi-use surgical instruments will be supplied non-sterile, to be steam sterilized by the user. The steam sterilizations for the system components were validated to assure SAL of 10^{-6}, and bioburden tests are conducted periodically.

Information regarding the sterilization of the implants and the cleaning and sterilization of the reusable surgical instruments is provided in the Investigator Brochure.

Regarding the ongoing OUS study - it is emphasized, that no device-related adverse events or device malfunctions were reported in any of the 47 patients implanted with the system. No failure was observed to any of the components implanted (about 180 pedicle screws (and locking elements), with about 90 rods for all 47 patients operated).

In addition, as indicated earlier, fusion - determined by X-Ray images indicating continuous fusion in between transverse processes and/or facet joints (AP and lateral X-Rays) – was indicated in the following rates (for the 40 DDD patients; please note

that for part of the patients, evaluation of translational and angular motion using flexion/extension radiographs was also conducted):

- At 6 months (1 level): 25/26 patients (96.2%);
- At 12 months (1 level): 3/3 patients (100%);
- At 6 months (2 levels): 1/1 (100%).

The on-going clinical investigation with the CarboClear device also supports the proper visualization of implant components, either during operation or at follow-up period. Also, no allergic reaction to the implant was reported.

As it is postulated, based on all the above, that the risk of device breakage/loosening/disassembly/migration; non/delayed fusion; or foreign body reaction to the device, would not be at a higher rate than seen for other cleared, rigid, pedicle screw systems, it is expected that the risk of re-operation due to these risks will be at similar rate as the rate reported for other pedicle screw systems.

On top of the above, all the operating instructions are described in the IFU and Surgical Technique documents (refer to **Appendix A**). The intended use, as well as inclusion/exclusion criteria for the clinical trial, are defined and detailed. The IFU (Package Insert) and Surgical Technique describe the safety and protective measures required when handling the system as well as providing a description of the system, all the procedures regarding system preparation, and operation procedures. Possible adverse events are described in the IFU. Relevant packing and sterilization data are also provided in the IFU as well as in the Company's Instrumentation Handling Instructions. The IFU and Surgical Technique provide specific information relating to implant selection and patient selection.

Safe use of the system with other devices is established by using items that comply with the requirements set in the Surgical Technique/IFU, where applicable, and in the manner detailed in the Surgical Technique. Reference is made in the Surgical Technique to the IFU and *vice versa*.

Please note, that the different components of the system (including surgical instruments), as well as the Surgical Technique and IFU, are designed in a similar manner, and include similar information to that provided with other pedicle screws systems available on the market. This further contributes to reducing the possibility of new hazards related to use of the system, and the risk of insufficient or inadequate information provided.

The IFU and Surgical Technique documents are reviewed prior to their release, and are approved according to the Company's procedures.

The device labels are also reviewed prior to their release, and are approved according to the Company's procedures. Wherever applicable, warnings regarding single use of components and the sterility of components are provided. The name of the component/content list, and catalogue and lot numbers are indicated on the items' labels as well.

5.14.3 POTENTIAL BENEFITS

In general, patients may not experience any direct benefits.

Based on the performance of other cleared pedicle screw systems that have successfully relieved symptoms of degenerative disc disease, and clinical experience with the investigational device outside the United States, there is reason to believe that the CarboClear Pedicle Screw System could also relieve DDD symptoms.

5.14.4 ADVERSE EVENTS

5.14.4.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device (including events related to the investigational medical device; and events related to the procedures involved).

Serious Adverse Event

Defined as one of the following events:

a. Death;

b. Serious deterioration in the health of the subject, that either resulted in:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - in-patient or prolonged hospitalization, or
   - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c. Event that led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect

Adverse event related to the use of an investigational medical device (including adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, and any event resulting from use error or from intentional misuse of the investigational medical device).

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (including malfunctions, use errors, and inadequate labeling).

Unanticipated Adverse Device Effect

Unanticipated adverse device effect means 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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5.14.4.2 Assessing and Reporting of Adverse Events

All adverse events, adverse device effects and device deficiencies (collectively: "Adverse Events") will be documented using the relevant Adverse Events Report Forms. In addition, each subject will be questioned about Adverse Events at each follow-up visit. Adverse Events discovered during a routine follow-up will be documented additionally on the relevant follow-up CRF.

Adverse Events occurring during the study will be treated by established standards of care that will protect the life and health of the study subjects.

Signs and symptoms of each Adverse Event should be described in detail and include start and stop dates, intensity, correlation with investigational device, action taken and outcome.

The Investigator shall evaluate and document the following:

1. whether any Adverse Events have occurred;
2. the nature of the event;
3. date of Adverse Event onset and duration;
4. seriousness of the event (serious, moderate, mild/minor);
5. relation to the investigational device (not related, possibly related, definitely related);
6. Adverse Event outcome and the course taken to reach the outcome.

The report of AEs based on specific type of event will be classified according to the following AE terms, listed in the table below, and in accordance with FDA list of risks applicable for pedicle screw spinal systems (FDA's Executive Summary, Table 11).

ADEVERSE EVENTS
Implant Malposition
Implant Loosening
Device Breakage
Construct Disassembly
Bone Fracture
Graft Settling/Displacement
Loss of Correction
Pseudoarthrosis
Bleeding/Vascular Injury
Neurologic Injury
Back/Leg Pain (Radiculopathy)
Dural Tear/CSF Leak
Wound problems
Infection/Sepsis
Skin Irritation
Cardiac
Respiratory
Gastrointestinal
Reoperation/Revision
Death

In addition, as per the FDA recommendation, the adverse events will be further classified according to the following Adverse Events table (as applicable to this study, *e.g.*, no control group):

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
All Adverse Events[1]															x (x %)	x	x (x %)	x
Operative Site/Implant/Spine Surgery Focused Events (Includes Perioperative Systemic Events Related to the Operative Site Occurring within 6 weeks of any spine procedure (initial or subsequent) at the index or adjacent level)																		
Implant (Total)																		
Breakage																		
Loosening																		
Migration																		
Malposition																		
Subsidence																		
Lumbar Spinal Event Target Level (Total)																		
Spinous Process Bone Erosion																		
Spinous Process Bone Reactive Change / Sclerosis																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Spinous Process Fracture																		
Facet Joint Degenerative Changes (Weishaupt)																		
Other (please specify in footnote)£																		
Lumbar Spinal Event Adjacent Contiguous Level																		
Lumbar Spinal Event Adjacent Non-Contiguous Level																		
Nonoperative Control Group Event																		
Nonunion (pseudarthrosis)																		
Intraoperative Events																		
Total																		
Anatomic/Technical Difficulty																		
Lumbar –Initial Surgery																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Lumbar – Subsequent Surgery																		
Device Unable to be Implanted																		
Intraoperative Device Revision																		
Dural Tear/Leakage																		
Intraoperative Vascular Injury																		
Anesthesia, Airway,Ventilation																		
Visceral Injury																		
Intraoperative Neurologic Injury																		
Intraoperative hypotension																		
Blood transfusion																		
Excessive blood loss																		
Major allergic reaction																		
Other (please specify in footnote)																		
Perioperative Systemic Events (Occurring ≤ 6weeks of operation)																		
Total																		
Deep vein thrombosis																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Pulmonary embolism																		
Retrograde Ejaculation																		
Anesthesia, Airway,Ventilation																		
Cardiac arrest/failure/arrhythmia																		
Myocardial infarction																		
Dysphagia																		
Dysphonia																		
Gastrointestinal bleeding																		
Pneumonia																		
Pressure sores																		
Urinary tract infection																		
CSF leak/meningocele																		
Sepsis unrelated to operative site																		
Other (please specify in footnote)																		
Post-Surgical Spinal Injections / Needle Based Procedures /Rhizotomies / Spinal Stimulators																		
Total																		
Epidural																		
Nerve root block																		
Facet Joint injection																		
Medial branch block																		
Sacroiliac injection																		
Trigger point																		
Rhizotomies																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Spinal Stimulators																		
Other (please specify in footnote)																		
Incision-Related, Non-Infectious (Lumbar)																		
Total																		
Posterior Lumbar Study Surgical Incision																		
Dehiscence																		
Hematoma																		
Hematoma Evacuation																		
CSF Leakage																		
Posterior Lumbar Non-Study Incision (Specify AE type)																		
Infection																		
Total																		
Superficial Wound – Posterior Lumbar Study Incision																		
Deep Wound – Posterior Lumbar Study Incision																		
Visceral / Organ space (Index level)																		
Superficial Wound – Posterior Lumbar Non-Study Incision																		
Deep Wound – Posterior Lumbar																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Non-Study Incision																		
Visceral / Organ space (Non-Index Spinal level)																		
Other (i.e., cellulitis, erythema)																		
Subsequent Surgical Interventions (Lumbar)																		
Total																		
Reoperation: Index level																		
Reoperation: Adjacent Contiguous Level																		
Reoperation: Index level and Adjacent Contiguous Level																		
Reoperation: Adjacent Non-Contiguous Level																		
Neurological†																		
Neurological																		
Total (Upper extremity)																		
Upper Extremity – Sensory																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Upper Extremity – Motor																		
Upper Extremity – Reflex																		
Total (Lower extremity)																		
Lower Extremity – Sensory																		
Lower Extremity – Motor																		
Lower Extremity – Reflex																		
Spinal Cord / Cauda Equina Disturbance																		
Upper extremity nerve compression (i.e. carpal tunnel)																		
Subjective*																		
Non-specific or Other**																		
Pain Events **Pain Events Considered as Spine-Related**																		
Cervical Spine/Upper Extremity Pain (Total)																		
Cervical Pain (Cervical Region)																		
Upper Extremity Pain																		
Combined Cervical and Upper Extremity Pain																		
Thoracic Pain (Thoracic Region)																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Lumbar Spine/Lower Extremity Pain (Total)																		
Low Back Pain (Lumbar Region)																		
Lower Extremity Pain																		
Combined Low Back and Lower Extremity Pain																		
Other (Non-Spinal) Pain																		
Total																		
Upper Extremity																		
Torso/Mediastinal																		
Lower Extremity																		
Headache																		
Abdominal																		
Pelvic																		
Other (please specify in footnote)																		
Musculoskeletal Events																		
Total																		
Cervical																		
Thoracic																		
Lumbar																		
Upper Extremity																		
Lower Extremity																		
Sacroiliac																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
Other (please specify in footnote)																		
Systemic Events (Total, Includes Systemic Events Occurring Within 6 Weeks of Index Surgery)																		
Total																		
Respiratory																		
Cardiac																		
Gastrointestinal																		
Infection (Systemic)																		
Cancer																		
Dermatologic																		
Urogenital																		
Ear, Nose, Throat																		
Hematologic																		
Endocrine																		
Hepatobiliary																		
Immunologic																		
Metabolism/Nutrition																		
Gynecologic																		
Opthalmologic																		
Psychological																		
Pregnancy																		
Surgical Procedure: Non-Spinal																		
Wound Infection (other f1spinal region: thoracic, cervical)																		
Wound Infection (non-spine related																		

	Surgery to Discharge		Discharge to Week 6		Week 6 to Month 3		Months 3 to 6		Months 6 to 12		Months 12 to 18		Months 18 to 24		Investigational group		Control Group	
Adverse Event Category	I	C	I	C	I	C	I	C	I	C	I	C	I	C	**#Subjects (% of xx)**	**Total Events**	**#Subjects (% of xx)**	**Total Events**
incision)																		
Incision-Related, Non-Infectious (other spinal region: thoracic, cervical)																		
Incision-Related, Non-Infectious (non-spine related incision)																		
Spinal Event Thoracic																		
Spinal Event Cervical																		
Other (please specify in footnote)																		
Death																		
Totals																		

Classification of Adverse Events by their seriousness and relationship to the investigational device shall be performed according to the following definitions.

Seriousness of Adverse Event

- **Serious Adverse Event** – an undesirable event that is fatal or life-threatening, or serious deterioration in the patient health that results in disabling (permanent impairment) or which necessitates prolonged hospitalization or medical or surgical intervention to prevent said life-threatening illness/injury or permanent impairment. Examples of serious adverse events are nerve root injury leading to significant and permanent paralysis, and vascular damage to major vessel.
- **Moderate Adverse Event** - an undesirable event that does not fall into any of the serious adverse event definitions, and that may cause non-severe deterioration in the patient health (without significant permanent harm); moderate adverse event may require medical or minimal invasive surgical intervention or prolonged hospitalization. Examples of moderate adverse events are seroma or hematoma that mandate drainage, or dehiscence mandating revision of wound.
- **Minor Adverse Event** – an undesirable event that did not result in any of the serious- or moderate adverse event outcomes, that is transient and does not lead to permanent disability or mandating prolonged hospitalization, invasive intervention, or prolonged medical treatment. Examples of minor adverse events are post-operative fever that resolved spontaneously, or wound problem that does not mandate drainage or surgical intervention.

Device Relatedness

An assessment regarding the causal relationship between the investigational device and an adverse event (device relatedness) should result in classifying the adverse event as Definitely Related-, Possibly Related-, or Unrelated to the investigational device, as hereby described.

- **Definitely Related** - The adverse event is clearly related to the investigational device, and no alternative cause is present. Such events may be due to device malfunction or direct injury of the device to the surrounding tissue.

- **Possibly Related** - There is a reasonable possibility that the adverse event may have been caused by or is linked in a significant way to the investigational device, but an alternative cause is present.
- **Unrelated** - The adverse event is clearly not related to the investigational device, and an alternative cause is present. Such events may be associated with the surgery and general anesthesia or hospitalization, *e.g.*, not related to the anatomic surgical site.

In addition, an independent Clinical Events Committee (CEC) will be established, to review all Adverse Events and determine the following:

a) Appropriate category for Adverse Events;
b) Severity, including whether or not the event should be classified as life-threatening;
c) Relationship to the device;
d) Relationship to the procedure.

The CEC will be composed of three members, US orthopedic surgeons, experienced in lumbar spinal fusion and pedicle screws fixation, who had conducted in the past similar clinical studies and similar adverse events evaluations.

All Adverse Events shall be reported to the Sponsor at: Fax: +972-9-9548939; Tel: +972-9-9511511; E-mail: hila@carbo-fix.com. This shall be done as soon as possible and no later than 5 working days after the event was first discovered. In case of a verbal report, a written notification, using the relevant CRF (Adverse Events Report Form), shall be followed within 5 calendar days.

Serious adverse events, serious adverse device effects, and device deficiencies that could have led to a serious adverse device effects should be reported to the Sponsor within 24 hours after knowledge to the Investigator or any study-related study center staff. Verbal report shall be followed by a detailed written notification within two calendar days, using the relevant form in the CRF.

Language of the reports shall be English.

The Sponsor is responsible for the classification of Adverse Events and ongoing safety evaluation of the clinical investigation, and shall review the Investigator's assessment of all Adverse Events and determine and document in writing their seriousness and relationship to the investigational device.
In case of device deficiency, the Sponsor shall determine and document in writing whether it could have led to a serious adverse device effect.
The Investigator shall supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

The Sponsor shall report to the Institutional Review Board (IRB), or ensure the reporting by the Investigator, of serious adverse events, serious averse device effects, and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the IRB/EC. Where required, the Sponsor is responsible for reporting such events to the relevant regulatory authorities.

5.15 INFORMED CONSENT

Each subject enrolled into the study must give a written and signed informed consent to participate in the study, prior to entrance into the study.
Each subject must be informed about the investigation, and must sign and date, prior to any procedure specific to the clinical study applied to him/her, an Informed Consent Form, acknowledging that participation is voluntary and that the follow-up visits are essential to complete data collection. The Investigator shall also sign and date the Form.
The Investigator will carefully explain the research nature of the study to the subject, avoiding any coercion or undue influence on the subject to participate the study.
A copy of the signed Informed Consent Form will be given to the subject; the Investigator shall retain an original copy.
The IRB must approve the Informed Consent Form used.

The Informed Consent materials are provided in **Appendix E**.

5.16 CASE REPORT FORMS

The data reported on the Case Report Forms (CRF) shall be derived from source documents and be consistent with these source documents; any discrepancies shall be explained in writing.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

Examples of these original documents and data records include hospital records, clinical and office charts, laboratory notes, memoranda, patients' evaluation checklists, recording media such as DVD, x-rays, patient files, and records kept at the laboratories.

The Investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

All data requested on the CRFs must be recorded. Missing data shall be explained. The CRFs shall be filled in English, and signed and dated by the Investigator. Any change or correction to data reported on a CRF shall be dated, initialed and explained if necessary, and shall not obscure the original entry.

The Case Report Forms (as well the Patient Questionnaires) are provided in **Appendix F**.

5.17 CONFIDENTIALITY

The privacy of each subject participating in the study and confidentiality of his/her information shall be preserved. The patient's full name will be removed from any study document to maintain confidentiality. Subject number and initials will identify patients. Data shall be secured against unauthorized access.

5.18 MONITORING

Monitoring of the study will be performed according to the Sponsor's approved monitoring procedures.

The Sponsor shall appoint a monitor to oversee the clinical study. The monitor shall be qualified by training and experience to monitor clinical studies, and shall be knowledgeable on the use of the investigational device, as well as the relevant regulation and requirements, the investigational plan, and the informed consent process. Training of the monitoring shall be documented in the Sponsor's files. The monitor may be an employee of the Sponsor or an independent contractor consultant.

The Sponsor, together with the monitor, will set a specific plan for the conduction of monitoring activities and schedules. This plan may be modified during study progression as deemed necessary by the Sponsor and monitor, based on the monitor periodic site visits/communication reports.

Prior to initiation of the study, the monitor will visit or otherwise contact each site of the clinical investigation and will assure that the Investigator:

1. has adequate qualifications;
2. understands the investigational status of the system and the investigational plan;
3. understands and accepts the obligations related with conducting the clinical investigation and the requirements set by the applicable regulations;
4. understands and accepts the obligation to obtain IRB approval prior to initiation of the study and the obligation to notify the Sponsor of any changes to that approval status;
5. signed the Investigator Agreement and forwarded a signed copy to the Sponsor;
6. understands and accepts the obligation to obtain an informed consent according to the relevant regulations;
7. has the adequate number of subjects suitable for the project, adequate facilities and resources, and sufficient time to carry the responsibilities of an investigator; and
8. was (with his/her team) trained for the use of the investigational device;

9. understands the importance of a timely report of any adverse events.

The monitor will be responsible for ***initiating the study*** and verifying that all the protocol and regulatory authority requirements are met prior to the initiation of the study (*e.g.*, the study protocol and other study documents were received and are understood to the investigator and his/her staff; the investigator and his/her team were trained for the use of the investigational device and are familiar with the investigator responsibilities, *etc*.).
Upon site initiation, a log shall be established identifying names, initials, signatures, functions, and designated authorities for the investigator and members of the investigation site team. In addition, a log for patient identification shall be issued.
The findings of the study initiation visit shall be documented

During the course of the investigation, the monitor shall conduct periodic monitoring visits, and where applicable discussions, to the investigational sites, according to predetermined schedule or as required. During those visits, the study monitor shall audit the site and shall verify that:

1. the facilities are still acceptable for the study;
2. the study Protocol/Investigational Plan, requirements of relevant International Standards, regulations and regulatory authorities (*e.g.*, FDA), any condition imposed by IRB, and the Investigator Agreement, are being followed;
3. any Protocol changes have been reported to the Sponsor and the IRB, and have been approved by the IRB, and, where applicable, other regulatory authorities;
4. accurate, complete and current records are maintained and are consistent with source documents;
5. special care should be taken to verify that the Informed Consent Forms are completed and signed accurately (*i.e.*, signed and dated informed consent forms have been obtained at the point of enrolment or before any clinical-investigation-related procedures were undertaken), and that adverse events are carefully monitored and reported;

6. reports to the Sponsor and to the IRB are accurate, complete and made in timely manner;
7. appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary, and initialed by the Investigator (or by his/her authorized designee); the monitor shall not make corrections, additions or deletions to the CRFs;
8. the Investigator has not delegated activities to other staff which were not specified and authorized previously;
9. the investigational device is being used according to the protocol and Instructions for Use and that, where modifications are required to the device or its method of use, these are reported to the Sponsor;
10. storage and investigational device accountability are correct and the traceability process is being followed;
11. the investigator continues to have access to an adequate number of subjects and investigational devices;
12. the investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation;
13. any corrective and preventive actions, as needed, have been implemented and are effective.

During the audit, study monitor may request study records, including source documents (individual subjects' records) for inspection and copying, and will compare them to the contents of reports made to the Sponsor by the Investigator to assure accuracy and completeness of the data. Any deficiencies noted will be corrected on site, if possible, according to correction instructions and adding the correct information. The correction shall be signed and dated by the Investigator. The finding of deficiencies may call for a review of a larger number of files or to rescheduling of the monitoring visits. Such decisions and the rationale for them will be recorded on the report made by the monitor to the Sponsor.

In general, the said comparison will ensure that:

i. the information recorded in the Investigator’s report to the Sponsor is complete, accurate and legible;
ii. there are no omission of data elements in the reports;

iii. missing visits and data elements are noted as such in the reports;
iv. subjects failing to complete the study and the reason for that are documented in the reports;
v. informed consent is documented in accordance with the relevant regulations.

The Investigator guarantees direct access to the study files, patient CRFs, and patient medical records, to staff of the Sponsor/monitor.

The last monitoring visit to the site shall be the ***Site Closure/Study Termination Visit***, during which the monitor shall verify, in addition to all the above, that the Investigator records are complete, all documents needed for the Sponsor's files are retrieved, and previously identified issues have been resolved. In addition, the monitor shall verify that the Investigator returned all the devices to the Sponsor, according to the Sponsor instructions, unless this action would jeopardize the rights, safety or welfare of the subjects.

The findings of the study periodic and last monitoring visits shall be documented.
All monitoring activities shall be forward in a written report to the Sponsor. A copy of the monitoring report or a summary of key findings shall be shared with the Investigator in writing. The records will include, at a minimum, the following information:

1. date of the visit;
2. name of the monitor;
3. Investigator and site visited details, and of any other staff members present at the visit;
4. a summary of the findings, conclusions, and any actions taken to correct any deficiencies noted during the visit.

The monitor shall ***document and maintain*** a copy of all the records and reports of each visit/audit or other contact/communication with the site and Sponsor during the investigation and for a period of 2 years after the latter of the following: (i) the date on which the investigation is terminated or completed; or (ii) the date that the records

are no longer required to support a regulatory notification to the authorities for the purpose of receiving a marketing clearance for the system in question.

Adverse events resulting from malfunction of the Investigational Device, or any other clinical complications, should be reported to the Sponsor/study monitor as described above (see **Section 5.14.4.2**).

In case of any unanticipated adverse device effect, the Sponsor shall immediately conduct an evaluation.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, the Sponsor shall suspend the clinical investigation while the risk is assessed.

The Sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed (*e.g.*, in case the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects). The termination will occur within 5 working days after the decision to terminate the study is taken and no later than 15 working days after first becoming aware of the adverse event. If the suspension or premature termination was in the interest of safety, the Sponsor shall inform all other investigators.

If resumption of the suspended study is desired – the Sponsor shall notify the investigator and the IRB (and if relevant – the regulatory authority) and provides them with the rational and supporting data. Study resumption shall be only following a written approval of the IRB. In the USA, resumption of terminated study is subjected to the regulation of CFR 21 part 812.46(c).

The monitor shall immediately (and no later than 5 days following the discovery of such an occurrence) notify the Sponsor of any ***conditions of non-compliance*** with the signed Agreement, Protocol, Investigational Plan, conditions of IRB, FDA and/or other regulatory authority approval and/or regulations. In case compliance cannot be secured, the Sponsor will discontinue shipments of the device to the non-complying investigator and terminate its participation in the investigation. The Sponsor shall also require such an Investigator to return the devices, unless this action would jeopardize the rights, safety, or welfare of a subject.

5.19 OPERATIONAL ISSUES

5.19.1 TRAINING

Investigators should be fully experienced with the use of pedicle screw systems and interbody fusion devices, and the required specialized spinal surgery techniques.

Training of the investigating team regarding the investigational device and the study Protocol will be provided by the Sponsor personnel or its authorized representative(s) prior to commencing any study-related procedure.

In particular, training of the Investigator will include a lecture and demonstration (possibly electronically), as well as simulation of the use of the system in sawbones, according to the Training Protocol (**Attachment D**). Training, and Investigator competency with the device and compliance with training, will be documented.

5.19.2 SUPPLY AND STORAGE (ACCOUNTABILITY)

The Sponsor will supply the CarboClear System (implants and surgical instruments), for the performance of the procedures within the scope of this study, for as long as the study is carried.

The CarboClear System shall be used only in the clinical investigation and according to this Protocol.

The Sponsor shall keep records to document the physical location of all investigational devices to the investigation sites until return or disposal.

All investigational devices received and used by the Investigator will be inventoried and accounted for throughout the study. The devices will be stored in a secure area with restricted access, separate from other medical devices. When instructed by the Sponsor, the Investigator will return any remaining devices to the Sponsor. The Investigator will not supply the investigational device to any person except those designated by him/her as co-investigator(s). If a device is explanted from a patient for any reason, it should be returned to the Sponsor following instructions provided by the Sponsor and/or the study monitor.

The Investigator shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following details:

1. Date of receipt;

2. Identification of each investigational device (*e.g.*, lot number);
3. Date of use;
4. Subject identification;
5. Date of return of unused, expired or malfunctioning investigational devices, if applicable.
6. Date of investigational device disposal, if applicable.

5.19.3 TRACEABILITY OF DEVICES AND DOCUMENTS

Complete traceability of all devices will be maintained during the study. Records will include raw materials, manufacturing and inspection data, as well as implantation data.

All documents and data shall be produced and maintained in a way that assures control and traceability. All documents, and subsequent versions, related to the clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation.

Each device shall be assigned with a lot number. The Sponsor will be responsible for product delivery, monitoring (CRF, *etc*.) and traceability records.

The investigational site shall maintain a log of all the subjects enrolled in the clinical investigation, assigning an identification code linked to their name. The Investigator will also maintain product inventory with traceability records and subject records.

5.19.4 RECORD RETENTION

Records related to the clinical study are subject to inspection by regulatory authorities and must be retained by the Sponsor and Investigator for a period as per regulations. The files may be discarded only upon notification from Sponsor.

The Investigator is responsible for retention (and where applicable, for the preparation, review and/or signing) of the following records:

- ✓ All correspondence, which pertain to the investigation;
- ✓ Device use/disposition and accountability records (as detailed above);
- ✓ Subject's case history records, including:

a. Signed Informed Consent Form;
b. All Protocol required evidences/observations;
c. Observations of adverse events;
d. Medical history;
e. Documentation of the dates and reasons for any deviation from Protocol;
f. Case Report Forms (CRFs):
g. Patient Questionnaires.

5.19.5 AMENDMENTS

The Protocol, CRFs, Informed Consent Form and other subject information, or other clinical investigation documents, may be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. The version number and date of amendments shall be documented.

Proposed amendments to the Protocol shall be agreed upon between the Sponsor and Principle Investigator, and the Sponsor shall incorporate the amendment into the document. The amendments to the Protocol and the subject's Informed Consent Form shall be notified to the IRB by the Sponsor, or approved by the IRB (and regulatory authorities, if required).
Non-substantial changes that do not affect the rights, safety and well-being of human subjects, or that are not related to the clinical investigation objectives or endpoints, should be simply notified to the IRB.

5.19.6 DEVIATIONS FROM PROTOCOL

The Investigator is not allowed to deviate from the Protocol, except as specified below.
Request for deviation from Protocol shall be agreed between the Sponsor and Investigator and communicate to the IRB by the Sponsor.
Under emergency circumstances, deviations from the Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the

Sponsor and the IRB. Such deviations shall be documented by the Investigator and reported to the Sponsor as soon as possible and to the IRB.

5.19.7 PUBLICATION

The results of this study may be submitted for publication. In case the study results are published, the participating subjects' identity will not be disclosed.

The ownership of the data shall, at all times, be held by the Sponsor.

The Sponsor reserves the right to include the report of this clinical investigation in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Upon approval by the Sponsor, Investigators are permitted to present the data at symposia, professional meetings, and to publish in journals, theses or dissertations methods and results of the study. Investigators agree to delay presentation or publication of study results until agreed to by all contributing centers, and by the Sponsor.

APPENDICES

Appendix A – Surgical Technique

Appendix B – Control Table

Appendix C – Training Protocol

Appendix D – Radiographic Protocol

Appendix E – Patient Informed Consent

Appendix F – CRFs and Patients Questionnaires