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NOV 21 2018

RMC IRB

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NOV 21 2019

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**A Comparison of Stryker's Tritanium® Posterior Lumbar Cage and PEEK Implant
on Spinal Fusion in Patients with Degenerative Disc Disease**

Protocol Identifying Number: RMC # 193

Principal Investigator: Juan Jimenez, MD

Sponsor: Stryker Spine

Funded by: Stryker Spine

Version Number: 1.0

September 21, 2018

1. Key Roles

1.1. Principal Investigator: **Juan Jimenez, MD**

Juan Jimenez, MD is a board-certified neurosurgeon, is qualified, and has the privileges to perform the surgical procedures described in this protocol.

1.2. Co-Investigator(s): **Charles Harvey, MD; Arun Jagannathan, MD; Jeff Coto, DNP, MS, RN, CCRN**

Charles Harvey, MD is a board-certified neurosurgeon, is qualified, and has privileges to perform the surgical procedures described in this protocol.

Arun Jagannathan, MD is a board-certified diagnostic radiologist and is qualified to evaluate CT and X-ray imaging; however, to minimize bias, two different board-certified diagnostic radiologists who are blinded to the study hypotheses will evaluate spinal fusion post-implantation.

Jeff Coto, DNP, MS, RN, CCRN, is an Assistant Professor of Nursing at Valparaiso University; his previous research experience makes him qualified to perform statistical analyses and interpret inferential statistics.

1.3. Sub-Investigator(s): **Brant Balthazor, PA; Kristin Balthazor, PA; Karim Bouferrache, PA**

1.4. Study Staff: **Joseph Hanks, BS**

1.5. Institution: **Riverside Medical Center**

2. Introduction: Background Information and Scientific Rationale

2.1. Background Information

2.1.1. Study Device

Tritanium PL Cage

The Tritanium Posterior Lumbar (PL) Cage is an Intervertebral Body Fusion implant intended for use as an aid in lumbar spinal fixation. This hollow, rectangular implant is offered in a variety of lengths, heights, widths and lordotic angles to adapt to a variety of patient anatomies. It has serrations on the superior and inferior porous surfaces of the implant for fixation, an ergonomically shaped anterior edge, and a flat posterior edge. The Tritanium PL Cage is manufactured out of Titanium Alloy Ti6Al4V (ASTM F1472).

Regulatory Status

United States:

- The Stryker Spine Tritanium PL cage is an intervertebral body fusion device indicated for use with autograft and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft when used as an adjunct to fusion in patients with degenerative disc disease (DDD) at one level or two contiguous levels from L2 to S1.
- DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies. The DDD patients may also have up to Grade I spondylolisthesis at the involved level(s).
- These patients should be skeletally mature and have six months of nonoperative therapy.

- Additionally, the Tritanium PL Cage can be used as an adjunct to fusion in patients diagnosed with degenerative scoliosis.
- The Tritanium PL Cage is to be implanted via a posterior approach.
- The Tritanium PL Cage is intended to be used with supplemental spinal fixation systems that have been cleared for use in the lumbosacral spine.

2.1.2. Clinical, Epidemiological, or Public Health Background

Degenerative Disc Disease (DDD)

Degenerative Disc Disease is the pain, weakness, or potential numbness that stems from a degenerated disc in the spine. Every person undergoes disc degeneration as they age; however, as one's spine is strained over time, the rigid outer shell of the disc weakens. As a result, the discs become less flexible and gradually collapses. In addition, a narrowing of the gap in the spinal column is observed. As the space between the vertebrae shrinks, additional pressure is placed on the discs, causing cracks or tears to appear. If the pressure is severe enough, it can force the jellylike fluid within the disc out through the tears, causing a herniated disc[Choi]. Diagnosis of DDD consists of an analysis of a patient's medical history, as well as a physical exam to reveal muscle weakness, tenderness, or poor range of motion. A CT myelogram, CT scan, discograph, or Magnetic Resonance Image (MRI) scan may be conducted to confirm the diagnosis[Taher].

Degenerative Scoliosis (DS)

Degenerative scoliosis describes a side-to-side curvature of the spine caused by degeneration of the facet joints and intervertebral discs of the spine. The condition is associated with "progressive and asymmetric degeneration of the disc, facet joints, and other structural spinal elements" and may result in "neural element compression" [Kotwal]. Accelerated degeneration of a skeletally mature and previously straight spine is characterized by "minimal structural vertebral deformities, advanced degenerative changes, and a predominance of lower lumbar curves" [Kotwal]. Symptomatic patients may be treated with nonsurgical interventions, such as physical therapy and exercises, chiropractic manipulation, and yoga; surgical treatments include "decompression of neural elements" and/or fusion in order to restore and stabilize the "sagittal and coronal balance" [Kotwal].

Spondylolisthesis

Spondylolisthesis is a condition in which a vertebra is mal-aligned in the sagittal plane with the vertebra below it, most often occurring in the lower lumbar spine. [Koreckj, TD]. The study devices are indicated for grade 1 spondylolisthesis, which accounts for approximately 75% of spondylolisthesis cases. Pain is described as intermittent and localized to the lower back, exacerbated by flexion and extension. Other symptoms include pain in the buttock region, numbness in the lower extremities, and/or loss of bowel and/or bladder control [Koreckj, TD]. Though conservative therapies like nonsteroidal anti-inflammatory drugs and exercise can be used to treat spondylolisthesis, severe cases often warrant surgical treatment, including decompression and/or fusion [Sansur].

2.1.3. Importance of the study

2.2. Scientific Rationale

Pain originating from the spine is the second most frequent cause for visits to a physician and “ranks fifth as the reason for hospital admission”^[6]. The Agency for Healthcare Research and Quality published a brief that found spinal fusion was the 6th most frequently performed surgical procedure with about 490,000 cases performed annually [[Holsgrove](#)].

It is hypothesized that the Tritanium PL Cage will result in satisfactory spinal fusion time in patients aged ≥ 21 years with degenerative disk disease and undergoing a spinal fusion in a one level or two contiguous levels from L2 to S1 compared to those who received PEEK implant as measured over a 6-week, 3-month, 6-month and 12-month post-operative period.

It is also hypothesized that participants implanted with the Tritanium PL Cage will report more improved back pain scores as measured by the Visual Analogue Scale (VAS), Oswestry Disability Index (ODI), 36-Item Short Form Survey (SF-36), Generic Health Status Survey (EQ-5D), and Press Ganey Patient Satisfaction Survey.

2.3. Potential Risks and Benefits

2.3.1. Known Potential Risks

The potential immediate and long-term risks associated with surgical implantation of the Tritanium PL Cage or PEEK implant are similar to other surgical procedures used to treat spinal instability and deformity. Risks associated with any surgical procedure include:

- Adverse reaction to anesthesia
- Hematoma or seroma at the operative site
- Failure to improve
- Persistent or worsened pain
- Infection of the wound
- Radiation exposure
- Wound dehiscence
- Vascular disorders, including thrombus
- Bronchopulmonary disorders, including emboli
- Genitourinary disorders
- Pneumonia
- Hemorrhage
- Myocardial infarction
- Paralysis
- Death

In addition to the potential risks associated with general surgical procedures, patients who are implanted with the Tritanium PL Cage or PEEK implant may also be at risk for the following:

- Loss of proper spinal curvature, correction, height, and/or reduction
- Delayed union or nonunion

- Neurological and spinal dura mater lesions from surgical traumaInfection or inflammation
- Nerve damage
- Paralysis
- Instrument failure resulting in a complication
- Allergic reaction to implanted materials
- Decrease in bone density due to stress shielding
- Dural leak requiring surgical repair
- Peripheral neuropathies
- Heterotopic bone formation
- Loss of bowel or bladder function

2.3.2. Known Potential Benefits

The expected potential benefits of spinal fusion using the Tritanium PL Cage or AVS UniLIF PEEK Spacer System are:

- Decrease in pain
- Improvement in back function
- Improvement in ability to work
- Improvement in ability to walk
- Improvement in health-related quality of life related to pain

3. Objectives and Purpose

3.1. Primary Objective

The primary purpose of this study is to measure the efficacy of the Tritanium Posterior Lumbar Cage, by examining how robust the fusion is and how long it takes to achieve fusion of the spine. The results of this study may demonstrate that the Tritanium PL Cage is an effective option for patients that suffer from DDD.

3.2. Secondary Objective(s)

The secondary objectives of this study are to:

- Compare participants' pre-surgical and post-surgical VAS, ODI, EQ-5D, and SF-36 scores to determine whether treatment with Tritanium or PEEK yields faster pain and quality of life improvement.
- Monitor device safety by gathering adverse event reports

4. Study Design and Endpoints

4.1. Description of the Study Design

This is a randomized, prospective, interventional, double-arm, single-blind, single-center, post-market study conducted to evaluate the difference in fusion rate and speed between Stryker's Tritanium PL Cage and Stryker's AVS UniLIF PEEK Spacer System.

4.2. Study Endpoints

4.2.1. Primary Endpoint

This study's primary endpoint is time to fusion at post-operative follow-up, evaluated by radiologist interpretation of radiographic and CT imaging.

4.2.2. Secondary Endpoint(s)

The secondary endpoints are:

- Improvement in lower-back and leg pain VAS score at follow-up visits
- Improvement in ODI at follow-up visits
- Improvement in Quality of Life as measured by the SF-36 and EQ-5D at follow-up visits
- Serious adverse events
- Proportion of participants using narcotics
- Proportion of participants returning to work
- Proportion of participants relying on assistive ambulatory device
- Proportion of participants requiring revision/secondary surgical intervention

5. Study Enrollment and Withdrawal

5.1. Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Subject is skeletally mature.
- Subject has one or more of the following diagnoses:
 - Degenerative disc disease (DDD) at one level or two contiguous levels from L2 to S1.
 - DDD may also include up to Grade I spondylolisthesis at the involved level(s).
 - Note: DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies.
 - Degenerative scoliosis for which the Tritanium PL cage will be used as an adjunct to fusion.
- Subject has received six months of non-operative therapy.
- Subject understands the conditions of enrollment and is willing to sign and date the Informed Consent.
- Subject agrees to comply with visit schedule and study assessments.
- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study

- In good general health as evidenced by medical history.

5.2. Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Subject is older than 75
- Subject is younger than 21
- Subject is an obese (BMI > 40) patient, as that can produce loads on the spinal system which can lead to failure of the fixation of the device or to failure of the device itself.
- Subject is sensitive to titanium materials.
- Subject has an active infection at the operative site.
- Subject has marked local inflammation.
- Subject has any abnormality present which affects the normal process of bone remodeling including, but not limited to, severe osteoporosis involving the spine, bone absorption, osteopenia, primary or metastatic tumors involving the spine, active infection at the site or certain metabolic disorders affecting osteogenesis.
- Subject has any mental, trauma, or neuromuscular disorder which would create an unacceptable risk of fixation failure or complications in postoperative care.
- Subject has any open wounds.
- Subject is pregnant or plans to become pregnant during the course of the study.
- Subject has inadequate tissue coverage over the operative site.
- Subject has any neuromuscular deficit which places an unsafe load level on the device during the healing period.
- Subject has any condition of senility, mental illness, or substance abuse.
- Subject has any other medical or surgical condition which would preclude the potential benefit of spinal implant surgery, such as the presence of tumors, congenital abnormalities, elevation of sedimentation rate unexplained by other diseases, elevation of white blood cell count (WBC), or marked left shift in the WBC differential count.
- Subject has prior fusion at the levels to be treated.
- Subject is incarcerated.

5.3. Strategies for Recruitment and Retention

20 participants will be recruited for this study, and it is anticipated that 30 patients will need to be screened in order to reach the target enrollment. There is an anticipated accrual rate of 2 participants per month. Participants will be recruited from the office of Neurosurgery Consultants. The study synopsis will be provided on Riverside's research website; no other forms of advertisement are planned.

Due to the long-term participation involved in this research study, participants will be contacted and provided with visit reminders when their visit date is approaching. In addition, to incentivize attending follow-up visits, participants will be compensated \$25 per study visit in the form of a check.

5.4. Participant Withdrawal or Termination

5.4.1. Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Death
- Failure to follow-up
- Decision to withdraw informed consent
- Termination of the study

5.4.2. Handling of Participant Withdrawals or Termination

Participants who withdraw from the research study will still be scheduled for standard-of-care follow-up visits. The investigators will continue to perform protocol-specified follow-up procedures in order to capture adverse events, serious adverse events, and unanticipated problems. In addition, participants will be informed of which study device they received.

5.5. Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspecting or terminating party to <investigator, funding agency, the IND/IDE sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume after concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB and/or FDA

6. Study Procedures and Schedule

6.1. Study Procedures/Evaluations

6.1.1. Study Specific Procedures

6.1.1.1. Oswestry Disability Index

The Oswestry Disability Index (ODI) measures impairment of daily living activities due to back pain. Greater impairment is associated with higher scores. ODI will be collected at screening and at each study follow-up visit.

6.1.1.2. SF-36

The Short Form Health Survey (SF-36) is a set of generic, coherent, and easily administered quality-of-life measures that rely upon patient self-reporting. This measure is utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

6.1.1.3. EQ-5D

EQ-5D is a standardized health-related quality of life instrument that can be used in a wide range of health conditions and treatment. The instrument assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D with 5 levels of severity for each of the 5 dimensions will be utilized in this study.

6.1.1.4. Lumbar X-Ray with Flexion/Extension

X-rays with flexion/extension will be obtained at baseline and at each follow-up visit interval (6-weeks, 3-months, 6-months, and 12-months). The x-ray technique is described in the **Radiographic Guidelines** section of this protocol. X-rays will be evaluated by two board-certified diagnostic radiologists who are blinded to the study's hypotheses and objectives.

6.1.1.5. CT Scan

Low-dose CT imaging of the index level(s) will be obtained at each follow-up visit interval (6-weeks, 3-months, 6-months, and 12-months). Parameters for performing the CT scan are provided in the **Radiographic Guidelines** section. The CT imaging will be evaluated by two board-certified diagnostic radiologists who are blinded to the study's hypothesis and objectives. Analysis of the CT scan is described in the **Radiographic Guidelines** section of this protocol, located in **Appendix B**.

6.1.2. Standard of Care Study Procedures

6.1.2.1. Radiologic Evaluation

An MRI scan will be used to determine the diagnosis under the surgeon's discretion. A lumbar plain x-ray with flexion/extension views will be obtained in cases of suspected spondylolisthesis.

6.1.2.2. Subject Demographics

Subjects' age, sex, height, weight, Body Mass Index (BMI), race, and ethnicity will be gathered.

6.1.2.3. Medical History

Medical history will be obtained by interview and from medical records and will be recorded by the Research Coordinator in study-specific case reports. Baseline medical history including spinal conditions, physical examination findings related to the subject's presenting condition, narcotic use, smoking status, and responses to quality of life and pain surveys.[sc1]

Current medication history will be recorded at each visit, and a review of medication history will be performed during eligibility assessment.

6.1.2.4. Physical Examination

Physical examination, musculoskeletal examination and neurological examination will be assessed.

6.1.2.5. Adverse Event Assessment

The PI will conduct an adverse event assessment at each follow-up visit to evaluate the safety of the implant. See section 8 **Assessment of Safety** for adverse event assessment and reporting procedures.

6.1.2.6. Ambulatory Status

The PI will record the date when the subject became completely ambulatory, defined as walking without any assistive device. Use of a cane, wheelchair, or walker will be recorded in the case report form at each visit.

6.1.2.7. Work Status

The PI will record whether the patient is working and indicate the hours per week of work that they are limited by back pain.

6.1.2.8. Visual Analog Scale (Leg Pain and Back Pain)

The subject will mark a spot along a visual analog scale corresponding to back pain experienced in the last two weeks, where 0 represents no pain and 100 represents worst imaginable pain. This will be completed at baseline and at each study follow-up visit. Subjects will be instructed to only focus on lower back pain. A separate VAS item will assess leg pain using the same method described above.

6.1.3. Standard of Care Surgical Procedure

Subjects will undergo the Transforaminal Lumbar Interbody Fusion (TLIF) procedure within 30 days of randomization unless there is a medically valid reason to postpone the surgery. A description of the surgical procedure is describe below, but a more thorough description is available in the **Surgical Technique Manual**, located in **Appendix A**. The PI and/or study coordinator will document key aspects of the surgical procedure in the study CRFs.

The entire procedure is done under fluoroscopic or image assisted guidance with patient in the prone position.		
Step 1	Exposure Open Approach	<ul style="list-style-type: none">• Patient is placed under anesthesia and positioned in the prone position
Step 2	Preparation of Facet Joints	<ul style="list-style-type: none">• Facet is prepared for fusion by removing the articular cartilage from the facet joint with a burr, rongeur, or other appropriate instrument.• Inferior and superior articular facets are removed on the side of the TLIF.
Step 3	Insertion Site Preparation	<ul style="list-style-type: none">• Tritanium PL cage may be inserted into the disc space using either a facet sparing or a transforaminal (TLIF) approach.• An osteotome or high-speed drill may be used to remove the inferior articular process of the cephalad vertebra; if an osteotome is used, it may be done with two cuts.• After both cuts are made, the inferior articulating process of the cephalad vertebra may be removed.• A curette may be used to release the ligamentum flavum from the superior lamina of caudal vertebra, allowing for distraction.• The ligamentum flavum may be preserved to minimize exposure of the neural elements.
Step 4	Distraction	<ul style="list-style-type: none">• Minimal distraction may be required to insert the implant.• Pedicle screw distraction, distraction between bony elements, and/or distraction with a positioning device may be used.• Distraction should be removed when the implant is in the interbody space to minimize external compressive forces on the interbody space.

Step 5	Discectomy	<ul style="list-style-type: none"> • Access to the disc space is achieved through an annulotomy made lateral to the posterior longitudinal ligament. • Vertical cuts are made parallel to the dura and laterally in the foramen from the endplate of the cephalad vertebra to the endplate of the caudal vertebra. • Additional cuts extend horizontally along the endplates of the vertebrae. • Access to the disc space may also be gained using an osteotome at the superior endplate of the lower vertebra.
Step 6	Sizing the disc space	<ul style="list-style-type: none"> • Disc space height is sized using a series of paddle distractors, reamer distractors, or trials. • Distractor size is serially increased until the appropriate fit within the disc space is achieved.
Step 7	Sizing	<ul style="list-style-type: none"> • A cage equivalent to the final Trial height or final distractor used is chosen. • Implant sizing is based on the fit and feel of either the final Trial or distractor.
Step 8	Assemble Cage	<ul style="list-style-type: none"> • Align the threaded distal tip of the Inner Shaft with the threaded hole on the selected cage. • Secure the cage to the Insertor by turning the knob on the Inner Shaft until the implant is tightly connected.
Step 9	Cage Insertion	<ul style="list-style-type: none"> • Cage is inserted gently and progressively into the disc space, using a mallet when necessary. • Optimal positioning may be facilitated by directing the implant obliquely.
Step 10	Placement of Bone Graft	<ul style="list-style-type: none"> • Autograft is placed in the interbody space prior to insertion of the implant. • Cage is filled with autograft prior to insertion, though additional bone graft may be placed lateral or dorsal to the implanted cage.
Step 11	Posterior Fusion	<ul style="list-style-type: none"> • Supplemental fixation of the lumbosacral spine will be obtained using Stryker's ES2 Spinal System inserted at this time, if not inserted earlier. • Compression of pedicle screws or interspinous device may be used to create segmental lordosis of the segment fused.
Step 12	Closure	<ul style="list-style-type: none"> • Foramen and TLIF site are checked for any bone fragments or extraneous tissue. • Wound is closed in a routine manner.

The following peri-operative data will be gathered from the participants' medical records and entered into the surgery case report form: Operating Room time, anesthesia time, estimated blood loss, length of stay, neurological complications, operative and postoperative complications, and cage size.

6.2. Laboratory Procedures/Evaluations

6.2.1. Standard of Care Clinical Laboratory Evaluations

The following tests will be performed for all patients prior to spinal fusion:

- Complete Blood Count
- Basic Metabolic Panel
- Methicillin-Resistant Staphylococcus Aureus
- Urinalysis with Reflex
- Type and Screen

The following tests will be performed for high-risk patients prior to spinal fusion:

- Electrocardiogram
- PT/PTT

6.3. Study Schedule

6.3.1. Screening/Enrollment/Baseline Visit

Patients will be screened against inclusion and exclusion criteria at conventional care visits. The patient's signature must be obtained on the informed consent form before performing any assessment that goes beyond the standard of care. A subject is enrolled in the study when the ICF is signed and the PI has determined that the subject meets all eligibility criteria.

Enrollment/Baseline Visit (Visit 1)

- Obtain informed consent of potential participant verified by signature on study informed consent form
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Provide participants with instructions on CT and X-ray follow-up schedule
- Obtain urine pregnancy test for women of child-bearing age who have not had a hysterectomy/or sterilization
- Obtain demographic information, medical history, medication history, diabetes status, chronic steroid use, and alcohol and tobacco use history
- Record vital signs, results of examinations, other assessments
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Explain study follow-up schedule.
- Schedule x-ray with flexion and extension

- Schedule surgical procedure for participants who are eligible and available for the duration of the study.

6.3.2. Follow-up Visit(s)

6-Week Follow-up Visit (Visit 2)

The 6-week follow-up visit must be performed between **35 and 49 calendar days post surgery**.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of physical examinations
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Record participant's adherence to treatment program.
- Obtain CT and X-ray of lumbar spine

3-Month Follow-up Visit (Visit 3)

The 3-month follow-up visit must be performed between **75 and 105 calendar days post-surgery**.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of physical examinations
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Record participant's adherence to treatment program.
- Obtain CT and X-ray of lumbar spine

6-Month Follow-up Visit (Visit 4)

The 6-month follow-up visit must be performed between **165 and 195 calendar days post-surgery**.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of physical examinations
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Record participant's adherence to treatment program.
- Obtain CT and X-ray of lumbar spine

6.3.3. Final Study Visit

Final Study Visit, 12-Month Follow-up Visit (Visit 5)

The 12-month follow-up must be performed between **350 and 380 calendar days post-surgery**.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of physical examinations
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Record participant's adherence to treatment program.
- Obtain CT and X-ray of lumbar spine

6.3.4. Early Termination Visit

If the participant is willing and it is not detrimental to his/her health, the study investigator should perform the following activities:

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Obtain participant's responses on VAS, ODI, EQ-5D, SF-36, and Press Ganey Patient Satisfaction Scale.
- Record participant's adherence to treatment program.
- Obtain CT and X-ray of lumbar spine

6.3.5. Unscheduled Visit

Unscheduled visits will be handled like scheduled visits if they fall within the study windows. A case report form will be filled out in the same manner as a scheduled visit, but it will be noted that the visit was unscheduled. The reason for the unscheduled visit must be recorded.

If the unscheduled visit falls outside of the study windows for a visit, the study investigator will provide conventional care (no study-specified CTs/X-rays will be obtained, no study-specific surveys will be administered). A CRF will be completed to monitor any change in participants' well-being. The reason for the unscheduled visit must be recorded.

6.3.6. Schedule of Events Table^[sc2]

7.3.8 Schedule of Events Table							
Procedure/Assessment	Screening / Baseline	Procedure	Discharge	6 Weeks	3 Months	6 Months	12 Months

Informed consent process, including informed consent signature	X						
Inclusion/Exclusion	X						
Demographics	X						
Physical Assessment and Vitals	X			X	X	X	X
Medical History	X			X	X	X	X
Medication History	X			X	X	X	X
Pregnancy test (urine)*	X						
MRI	X						
CBC, Basic Metabolic Panel, Methicillin-Resistant Staphylococcus Aureus, Urinalysis w/ Reflex, and Type and Screen	X						
Electrocardiogram and Prothrombin Time/Partial Thromboplastin Time**							
X-Ray w/ Flexion and Extension	X			X	X	X	X
Lumbar Spine CT	X			X	X	X	X
Visual Analog Scale (VAS)	X			X	X	X	X
EQ-5D	X			X	X	X	X
Oswestry Disability Index (ODI)	X			X	X	X	X
SF-36	X			X	X	X	X
Adverse Event		X	X	X	X	X	X

*For women of child-bearing potential

**For high-risk patients only

6.4. Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

6.5. Prohibited Medications, Treatments, and Procedures

Chiropractic care is discouraged; medications that interfere with bone deposition; chemotherapy; radiation to spine; and immuno-therapeutics

7. Assessment of Safety

7.1. Anticipated Adverse Events

The following anticipated adverse events (AE) for study subjects are identical to any other patient implanted with the Tritanium PL or PEEK Cage, regardless of study participation.

7.1.1. Table 8.1.1.: Potential Adverse Events for Implantation of the Tritanium PL or PEEK Cage

Anticipated Adverse Events for Implantation of the Tritanium PL Cage	
Late bone fusion	Peripheral neuropathies
No visible fusion mass	Nerve damage
Pseudarthrosis	Heterotopic bone formation
Implant weakening	Neurovascular compromise, including paralysis, loss of bowel, bladder function, or foot-drop
Superficial or deep-set infection	Spine growth cessation of the fused portion
Inflammatory phenomena	Loss of proper spinal curvature, correction, height, and/or reduction
Allergic reaction to implanted materials	Delayed union or nonunion
Decrease in bone density due to stress shielding	Neurological and spinal dura mater lesions from surgical trauma
Dural leak requiring surgical repair	Early loosening resulting from inadequate initial fixation, latent infection, premature loading of the device, or trauma
Bone Erosion	Late loosening resulting from trauma, infection, biological complications or mechanical problems
Pain	Distraction or stress shielding of the graft or fusion mass caused by inappropriate or improper surgical placement of device
Intraoperative fissure, fracture, or perforation of spine	Postoperative fracture of bone graft or the intervertebral body above or below the level of surgery due to trauma, the presence of defects, or poor bone stock
Spinal Surgery Complications	
Genitourinary Disorder	Gastrointestinal Disorder
Vascular Disorder, including thrombus	Bronchopulmonary Disorder, including emboli
Bursitis	Hemorrhage
Myocardial infarction	Infection
Paralysis	Death

7.2. Specification of Safety Parameters

All adverse events, serious adverse events, unanticipated problems, and device deficiencies will be recorded in the CRF. A safety report will be completed and signed by the PI, detailing the event. The report will entail a summary of the event, including the date of its occurrence and the location of occurrence; a narrative of the event; description of any actions taken in response to the event; the subject's participation status after the event; the subject's prognosis; the PI's evaluation of the event; the PI's judgement concerning the need to revise the study protocol; the PI's judgement regarding notification/re-consent of other subjects; and PI's decision on future study conduct.

7.2.1. Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

This definition includes events related to both the Tritanium PL Cage and PEEK implant and all procedures involved in this clinical investigation protocol.

7.2.2. Adverse Device Effect (ADE)

An adverse device effect is “any adverse event related to the use of an investigational medical device.” This definition includes events resulting from deficiencies or inadequacies in the instructions for use, the operation, the implantation, the installation, the deployment, or any malfunction of the medical device, including any event caused by use error or intentional misuse of the investigational medical device.

7.2.3. Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2.4. Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP and the investigators will consider the following corrective actions in the event that an UP is discovered:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

7.3. Classification of an Adverse Event

7.3.1. Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.3.2. Relationship to the Study Device

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE’s causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to device implantation and cannot be explained by concurrent disease or other drugs or chemicals.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal lab test result, occurs within a reasonable time after device implantation, is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after device implantation). However, other factors may have contributed

to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and may be upgraded as appropriate

Unlikely to be Related – A clinical event, including an abnormal lab test result, whose temporal relationship to device implantation makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after device implantation) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of the study device implantation, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

7.3.3. Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. The PI will indicate this on the adverse event report submitted to the IRB and study sponsor.

7.4. Time Period and Frequency for Event Assessment and Follow-Up

AEs and SAEs will be identified at scheduled follow-up visits and unscheduled visits made by the patient; in addition, AEs and SAEs will be identified when the PI is notified that the patient has entered the ED for any reason, utilizing Epic's "in-basket" feature. The PI will follow-up on all suspected AEs and SAEs on a weekly basis for 3 weeks following the discovery of the adverse event or until enough information is gathered to complete an adverse event report.

UPs will be recorded in the same manner that AEs and SAEs are reported; however, the following additional steps may be taken to ensure all subjects enrolled in the study are protected after the identification of an UP:

- If the presence of an unanticipated problem poses a safety risk for other participants, the Principal Investigator must ensure that all participants are re-consented with an informed consent form that reflects the acknowledgment of increased risk.
- If the unanticipated problem places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized, the study may be suspended until the risk has been addressed or the study may be terminated.

7.5. Reporting Procedures

7.5.1. Adverse Event Reporting

Any AE that occurs during the participant's enrollment in the study will be recorded on the AE case report form. Pre-existing medical conditions or symptoms occurring prior to the initiation

of the study will not be reported as AEs, but an exacerbation of a pre-existing medical condition or symptom will be reported as an AE. Pain, neurological status, and functional impairment should be considered AEs when a participant's complaint for any of these symptoms results in an unscheduled visit and/or when a participant presents with a new or worsening symptoms as compared to a previous visit. All AEs will be followed until the event is resolved or considered to be stable.

IF an AE is ongoing when the participant completes the final visit, the AE will be followed until resolution or until 3 weeks after the final study visit has passed, whichever comes first. The study files must contain relevant source documents to confirm the occurrence of an AE and must be provided to the IRB upon request.

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 7 calendar days of initial receipt of information	Investigator	<ul style="list-style-type: none"> Local/Internal IRB Stryker's Post Market Surveillance Team
		Sponsor or Designee	<ul style="list-style-type: none"> FDA (if IND study)
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 15 calendar days of initial receipt of information	Investigator	<ul style="list-style-type: none"> Local/Internal IRBs/Institutional Officials Stryker's Post Market Surveillance Team
		Sponsor or Designee	<ul style="list-style-type: none"> FDA (IND/Marketed Products) All participating investigators
Unanticipated adverse device effects	Within 10 working days of investigator first learning of effect	Investigator	<ul style="list-style-type: none"> Local/internal IRBs Stryker's Post Market Surveillance Team
		Sponsor or Designee	<ul style="list-style-type: none"> FDA (if IDE study)
Unanticipated Problem that is not an SAE	Within 14 days of the investigator becoming aware of the problem	Investigator	<ul style="list-style-type: none"> Local/internal IRBs/Institutional Officials Stryker's Post Market Surveillance Team
All Unanticipated Problems	Within 30 days of the IRB's receipt of the report of the UP from the investigator	IRB	<ul style="list-style-type: none"> OHRP
		Investigator	<ul style="list-style-type: none"> IRB

7.5.2. Serious Adverse Event Reporting

Describe the SAE reporting procedures, including timeframes. Include description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the SAE reports. Describe who will receive notification of SAEs.

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Section 8.1.2, Definition of Serious Adverse Event** must be submitted on an SAE form to the DCC if one exists for the study. If a study is overseen by a Data and Safety Monitoring Board (DSMB), the DSMB may request to receive real-time notification of all SAEs or only SAEs thought to be related to study agent.

According to 21 CFR 312.32(c)(1), “the sponsor must notify FDA and all participating investigators...in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Furthermore, according to 21 CFR 312(c)(2), “the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor’s initial receipt of the information.”

As noted previously, an unanticipated adverse device effect could be considered an SAE (**Section 8.1.2, Definition of Serious Adverse Event**). For IDE studies, according to 21 CFR 812.150(a)(1), “an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.” In addition, 21 CFR 812.150(b)(1), “A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB’s and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.”

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.

Other SAEs regardless of relationship, will be submitted to the DCC/study sponsor within 72 hours of site awareness

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in **Section 1, Key Roles**. The investigator and study sponsor are responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

7.5.3. Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 10 days the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 10 days of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

7.6. Study Halting Rules

Implantation of the study devices will be halted when three grade 3 AEs determined to be “probably related” are reported to the IRB. The PI will notify the study sponsor and IRB immediately when the third grade 3 event is reported and the investigators will stop accepting new study participants.

7.7. Study Oversight

Safety oversight will be under the direction of Riverside’s Institutional Review Board, composed of individuals with the appropriate expertise, including medical doctors, community members with a scientific background, and nurses. The IRB will conduct a comprehensive study audit and will meet at least semiannually to assess safety and efficacy data on each arm of the study. The IRB will provide its input to the study sponsor and study team.

8. Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring activities include communication with the clinical investigator and study site staff; review of the study site’s processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor.

Clinical monitoring will be conducted by both the study sponsor and Riverside’s IRB.

Riverside’s IRB will conduct the following monitoring activities:

- Annual audit of data collected from the study and study files
- Annual observation of informed consent process
- Monthly review of reported adverse events and protocol deviations and performance of risk assessment to determine the need for an action plan

Stryker Spine will conduct the following monitoring activities:

- Regularly scheduled audits at critical phases of the study
- Review of complaint submissions by Stryker representatives

9. Statistical Considerations

9.1. Statistical and Analytical Plans

The general statistical plan is outlined below. A detailed statistical analysis plan (SAP) will be developed and approved by the study sponsor and study principal investigator prior to analysis.

9.2. Statistical Hypotheses

Primary Efficacy Endpoint(s):

Spinal Fusion

- **Alternative Hypothesis:** Implanting the Tritanium posterior lumbar cage results in satisfactory spinal fusion time in patients aged ≥ 21 years with degenerative disk disease and undergoing a spinal fusion in a one level or two contiguous levels from L2 to S1 compared to those who received PEEK implant as measured over a 6-week, 3-month, 6-month and 12-month post-operative period
- **Null Hypothesis:** Implanting the Tritanium posterior lumbar cage does not result in ~~an~~ satisfactory spinal fusion time in patients aged ≥ 21 years with degenerative disk disease and undergoing a spinal fusion in a one level or two contiguous levels from L2 to S1 compared to those who received PEEK implant as measured over a 6-week, 3-month, 6-month and 12-month post-operative period

Secondary Efficacy Endpoints(s):

Questionnaires

- **Alternative Hypothesis:** Participants implanted with the Tritanium posterior lumbar cage will report higher quality of life improvement, pain improvement, and disability improvement scores compared to participants implanted with the PEEK AVS uniLIF Spacer System as measured over a 6-week, 3-month, 6-month and 12-month post-operative period
- **Null Hypothesis:** There will be no difference between the quality of life, pain, and disability scores in participants that were implanted with the Tritanium or PEEK AVS uniLIF Spacer System as measured over a 6-week, 3-month, 6-month and 12-month post-operative period

Adverse Events

- **Alternative Hypothesis:** There will be a difference in the number and severity of adverse events observed between participants who were implanted with the Tritanium posterior lumbar cage compared to participants who were implanted with the PEEK AVS uniLIF Spacer System as measured over a 6-week, 3-month, 6-month and 12-month post-operative period
- **Null Hypothesis:** There will be no difference in the number and severity of adverse events observed between participants who were implanted with the Tritanium posterior lumbar cage compared to participants who were implanted with the PEEK AVS uniLIF Spacer System as measured over a 6-week, 3-month, 6-month and 12-month post-operative period

9.3. Description of Statistical Methods

9.3.1. Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint analysis involves a comparison of participant fusion rates at 6-weeks, 3-months, 6-months and 12-months after surgical intervention. All participants who were enrolled will be included in this analysis. Participants will be excluded from the analysis if a CT scan and x-ray cannot be obtained at the 6-week visit.

9.3.2. Analysis of the Secondary Endpoint(s)

Improvement in SF-36, EQ-5D, ODI, and VAS scores will be compared between groups using a repeated measure ANOVA (analysis of variance).

The occurrence rate of adverse events will be assessed using a Kaplan-Meier approach and a comparison of serious adverse event rates will be made using a chi-squared analysis.

9.3.3. Baseline Descriptive Statistics

Descriptive statistics of all participants enrolled will be generated, including demographics and clinical diagnosis characteristics at baseline.

9.4. Measures to Minimize Bias

9.4.1. Enrollment/Randomization/Masking Procedures

Study participants will be assigned to study groups by permuted block random assignment at the enrollment visit after a study investigator has determined that the participant meets all inclusion criteria and no exclusion criteria. The study participants will be blinded to which group they have been assigned.

One potential bias that has been identified is the impact of knowing which device one has received on subsequent rating scales. Participants who are aware that they have been implanted with the Tritanium PL Cage may be more inclined to rate their pain as “improved.” To ensure participant survey responses are not confounded, participants will be blinded to which study group he or she is assigned.

Trial randomization codes will be tracked by the research coordinator by marking the designated section on study participants’ enrollment visit CRF. Planned unmasking will occur at the final study visit (12-month visit). Unplanned masking is defined as unmasking that occurs before the final study visit. If a study participant learns to which group he or she was assigned, it will be noted on his or her case report form that masking has been broken. The participant is still permitted to participate in the research study.

Another potential bias that has been identified is the radiologists’ interpretation of the CT and X-ray scans. Radiologists who are not informed of the study’s hypotheses will perform CT and X-ray evaluation to avoid bias in the interpretation of fusion rate. In addition, two radiologists will independently evaluate the fusion following the guidelines described in this protocol to establish inter-rater reliability.

No dummy techniques will be necessary, as patients will be unable to determine with which device they’re implanted. Epic will be utilized to inform other health care providers that the implanted device should not be revealed to the participant.

Study participants who discontinue early (at or before the 6-week study visit) may be replaced if the radiographic imaging was not performed.

9.4.2. Evaluation of Success of Blinding

Participants will be asked at each follow-up visit if he or she has become aware of which device he or she received. The research coordinator will record participants' responses in the CRF.

9.4.3. Breaking the Study Blind/Participant Code

Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for SAEs). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

The study blind will be broken when:

1. The participant leaves the study for any reason
2. A serious adverse event occurs and the Institutional Review Board determines it is necessary for all participants to know device they received

Intentional and unintentional breaking of the blind should be reported in the participant's case report form. If unintentional, a protocol deviation report must be filled out by the PI and submitted to the IRB.

9.4.4. Missing Data

In evaluating primary endpoints, missing radiographic data will be excluded from the analysis. If 6-week radiographic endpoints cannot be obtained, the participant will be removed from the study.

In evaluating secondary endpoints, the following methods will be followed for including missing endpoint values

- Last observation carried forward
- All missing data are worst possible response
- All missing data are best possible response

10. Source Documents and Access to Source Data/Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant' memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

11. Quality Assurance and Quality Control

The study team will follow SOPs on data entry and storage. Any missing data or data anomalies will be communicated to PI for clarification/resolution.

The study team will follow SOPs on staff training requirements, and a training tracking log will be maintained by the Research Coordinator and stored in the study binder.

Following written SOPs and protocol, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12. Ethics/Protection of Human Subjects

12.1. Ethical Standard

The principal investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56.

12.2. Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Riverside Medical Center IRB for review and approval. Approval of both the protocol, consent form, and any recruitment materials must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the RMC IRB before the changes are implemented to the study. All changes to the consent form will be RMC IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3. Informed Consent Process

12.3.1. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families, if present. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with friends, family, or their physician, or think about it prior to

agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the study sponsor. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

13. Data Handling and Record Keeping

13.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.**

Copies of the CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into paper case report forms. Clinical data will be entered directly from the source documents.

13.2. Study Records Retention

Study documents must be retained for a minimum of 3 years after the study's closure. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. All deviations must be addressed in study source documents. Study deviations must be sent to the IRB per Riverside's guidelines. The site PI/study staff is responsible for knowing and adhering to IRB requirements.

13.4. Publication and Sharing Policy

Riverside and the PI retain the right to publish information related to the study so long as such publication or other public disclosure does not and is not reasonably anticipated to result in Stryker's loss of rights in or to Confidential Information, or Research Inventions. Prior to submission for publication of abstracts, manuscripts, presentations or other communications describing the results of any aspect of the study the party seeking to publish shall send Stryker a copy of each manuscript to be submitted via email to SpineClinical@stryker.com, and allow Stryker at least forty-five (45) days to review a copy of the material intended for publications in order to redact any Confidential Information, or Research Inventions therefrom. Upon receipt of notice from Stryker Institution or Investigator shall expunge from any proposed publication or other public disclosure, and shall not publish or disclose, any information that Stryker reasonably believes would result in loss of rights in any Stryker Confidential Information, or Research Inventions or would otherwise compromise Stryker's rights or interests.

14. Study Administration

14.1. Study Leadership

The Study Team will govern the conduct of the study. The Study Team will be composed of the Principal Investigator, the Operations Director, the Investigators, and the Research Coordinator. The Study Team will work closely together to carry out study activities and ensure compliance with the study protocol.

14.2. Investigator Responsibilities

The PI is responsible for ensuring that the research study is conducted in accordance with the clinical investigation plan, conditions of approval set by the RMC IRB, state and federal regulations, and ethical guidelines, affording the most protection to the subjects enrolled in this research study.

The investigators agree to the following:

- The project will be performed by qualified personnel according to the RMC IRB-approved protocol.
- Make no changes or deviate from the research protocol, except to protect the life and physical well-being of a subject in an emergency; in the event of such a deviation, it will be documented and explained.
- The equipment, facilities, and procedures to be used in this research meet recognized standards for safety.
- No change will be made to the human subjects protocol or consent form(s) until approved by the RMC IRB.

- Create and maintain source documents throughout the research study; ensure that all study-related materials are retained per institutional and protocol requirements.
- No subjects will be enrolled or data collected until the study is approved by the RMC IRB, and unless approval is current.
- Legally effective informed consent or assent will be obtained from all human subjects as required.
- Record, report, and assess every adverse event in accordance to the protocol; and report to the RMC IRB and sponsor all SAEs and device deficiencies that could have led to an SAE.
- Unanticipated problems, adverse events, and/or new information that occur in the course of the investigation that may affect the risk-benefit assessment for this research will be reported to the RMC IRB Office.
- Inform subjects of any new significant findings that occur during the study and provide him/her with procedures for possible emergencies related to the study, and make the necessary arrangements for emergency treatment.
- All named individuals on this project have read and understand the procedures outlined in the protocol and will be acting under my supervision.
- All named individuals on this project have completed the applicable CITI training program with a score of at least 80% or greater on every module, and have been given an opportunity to review the Belmont Report and The “Common Rule” (45 CFR Part 46).
- Student and guest investigators on this project are knowledgeable about the regulations and policies governing this research.
- I have read and understand the information in the Indications For Use document and Surgical Technique Manual, including potential side effects and risks of the device.
- I agree to maintain adequate and accurate records in accordance with the regulations and to make those records available for inspection in accordance with the regulations.
- I agree to cooperate with the IRB in the event it audits any or all of my IRB approved protocols to inquire about study progress or to observe the consent process that is used.
- I agree to meet with the investigator(s), if different from myself, on a regular basis to monitor study progress.
- If I will be unavailable, as when on sabbatical or other leave, including vacation, I will arrange for an alternate medical staff sponsor to assume responsibility during my absence. I will advise the RMC IRB by letter of such arrangements.
- I agree to promptly and completely comply with an IRB decision to suspend or withdraw its approval for the project.
- I agree to submit a final report to the IRB upon conclusion of the project.
- If I, or my spouse, or dependent children have any significant financial interests* related to the work to be conducted as part of the project, including the pharmaceutical or medical equipment company and other entities whose financial interests would reasonably appear to be affected by the outcome of the study, I have disclosed them below.

*Significant Financial Interests: Income exceeding \$5,000 including salary, consultant payments, honoraria, royalty payments, dividends, loan, or any other payments or consideration with value. Equity in the form of stock, stock options, real estate, loan to, or any other investment or ownership interest exceeding \$5,000 (current market value) or a 5% or greater ownership interest. A management position (director, officer, partner, or trustee) with the interested entity.

14.2.1.1. Delegation of Responsibility

The PI is responsible for providing training and supervision of study team members who perform tasks that are delegated by the PI. The PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the research study.

15. Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the RMC IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All members of the Study Team will disclose whether he/she or his/her spouse or dependent children have any significant financial interests related to the work to be conducted as part of the project, including the pharmaceutical or medical equipment company and other entities whose financial interests would reasonably appear to be affected by the outcome of the study.

Appendix A: Radiographic Guidelines

GE Optima CT660

Type	Multislice
# of slices	64
GREEN FEATURES	≥60% lower CO2 emissions using energy-saving mode
DETECTOR	
Field of view	50
Total detector width, z-axis, mm	40
Optional minimum rotation time, sec	0.35
Standard Rotation times, sec, 360°	0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2
CLINICAL APPLICATIONS AND FUNCTIONALITY	
Z-axis coverage for brain perfusion	32 cm
GANTRY	
Gantry opening, cm	70
Gantry angle deg	
GENERATOR	
Ma range	10-600, 5 increments
kW output	0.8-72
Kvp range	80, 100, 120, 140
TABLE FEATURES	
Optional max load capacity, with restrictions, kg	227
Max load capacity without restrictions, kg	227
SYSTEM INTEGRATION	
DICOM	Yes
Storage commitment SCU	Yes
ECG waveform SCP/SCU	Yes
Query/Retrieve SCU and SCP	Yes
Modality worklist SCU	Yes
CT image storage SCU/SCP	Yes
Modality performed procedure step SCU	Yes
Enhanced CT storage SCU/SCP	Yes
IMAGE RECONSTRUCTION	
Archive	MiniSAS HDD, HDD
Computer cpu	Intel E5540 DUAL 2.53 GHz Quad Core Xeon Processors QPI
Reconstruction matrices	512 x 512
FDA CLEARANCE	Yes
CE MARK	Yes
MARKETING REGION	Worldwide

Criteria for evaluating spinal bony fusion

- No lucent area around the implant
- No presence of herniated disk, central stenosis, lateral recess stenosis, foraminal stenosis, facet arthropathy.
- No fracture of the device, graft, or vertebra
- Visible bone formation in or about the graft material
- Less than 3 degrees of inter-segmental position change on flexion and extension views
- Presence of subsidence: a migration of more than 3mm into the adjacent vertebra
- Proportion of bridging bone visually estimated over the surface area of the joint (i.e., 5%, 15%-30%, etc.).