Spine

AccuLIF® PROSPECTIVE PATIENT OUTCOMES STUDY

A prospective, post-market, multi-center study of the AccuLIF System

Sponsor: *Stryker Spine*

Study Product: AccuLIF®

Protocol Number: 2015-L-001

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Protocol Change History

Version	Description	Changed By
1.0	New	
1.1	Removed Flexion / extension x-rays at 6 months. Noted that 24 month CT may be collected for patients that did not demonstrate fusion at 12 months. Updated date and version number.	

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Study Synopsis

Title	A Prospective Multi-Center Evaluation of a hydraulic expandable TLIF cage for the treatment of Degenerative Disc Disease of the Lumbar Spine
Short Title	**APROPOS (A**ccuLIF® **Pro**spective **P**atient **O**utcomes **S**tudy)
Protocol Number	2015-L-001
Phase	Post-Market
Methodology	This is a prospective, post-market, multi-center, clinical evaluation of the AccuLIF expandable TLIF cage in patients requiring arthrodesis for degenerative disc disease (DDD) or DDD with up to Grade I spondylolisthesis or retrolisthesis at one or two contiguous levels between L2 and S1. DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies.
Study Duration	Enrollment period: approximately 9 months Study follow-up period: each subject will be followed for 24 months (2 years) Total study duration: approximately 36 months
Study Center(s)	Up to 10 centers in the US will participate
Hypothesis	It is hypothesized that patients implanted with the AccuLIF expandable TLIF cage will show restoration of anterior, middle, and posterior disc height, improve segmental lordosis and maintain regional and global sagittal balance post operatively. Primary success is defined as an increase of 3 degrees or more of segmental lordosis post operatively. It is also hypothesized that patients implanted with the AccuLIF expandable TLIF cage will show improvement in post-operative clinical outcomes when compared to pre-operative clinical status.

Objectives	**Primary:** • To compare pre-operative and postoperative radiographic outcomes of a cohort treated for lumbar degenerative disease at one or two contiguous levels implanted with the AccuLIF expandable TLIF cage via TLIF procedure with supplemental fixation. Primary Radiographic parameters are defined as: o Disc height (anterior, middle, posterior in millimeters) o Foraminal height o Segmental lordosis (at each TLIF level in degrees) o Regional Lordosis: (inferior endplate T12-S1 in degrees) o Sagittal balance: (C7-S1 in millimeters) • Primary success is defined as an increase of 3 degrees or more of segmental lordosis post operatively. **Secondary**: • To observe surgical parameters of the AccuLIF cohort. Defined as; operative time, estimated blood loss and length of stay. • To assess the occurrence of neurologic complications by comparing pre-operative and postoperative neurologic evaluation. • To assess clinical outcomes by comparing pre and post-operative patient measured outcomes defined as VAS, ODI and quality of life (QOL) as measured by SF-12 of the AccuLIF cohort. • To observe the occurrence and frequency of additional complications of the AccuLIF cohort, including infection and nonunion. • To observe standard radiographic outcomes defined as; fusion status, cage placement, migration / subsidence and parameters of supplemental fixation hardware including screw placement and subsidence.

	Exploratory: • To evaluate the percentage of subjects that achieve > 3° lordosis and no negative changes in regional lordosis and global sagittal balance. • To compare changes in disc height, lordosis, sagittal balance as categorized by disc morphology. Disc morphologies are defined as: ○ **Tall and lordotic** Average Disc Height ≥11 mm **AND** Disc Angle >12°. ○ **Moderate** Average Disc Height ≥7 mm to ≤10 mm **AND** Disc Angle ≥5° to ≤12°. ○ **Flat and compressed:** Average Disc Height 0 mm to ≤6 mm **AND** Disc Angle 0° to <5°. • To compare summary AccuLIF data to published literature of comparable TLIF outcomes.
Number of Cases	Approximately 100 subjects will be enrolled in this study.

Diagnosis and Main Inclusion/Exclusion Criteria	Inclusion criteria: 1. Subject is skeletally mature and between 18 and 70 years of age. 2. Subject has one or more of the following diagnoses: DDD or DDD with up to Grade I spondylolisthesis or retrolisthesis, requiring decompression and arthrodesis at one or two contiguous levels between L2 and S1 as confirmed by CT, MRI, myelography and/or lateral flexion/extension films. 3. Subject has not previously undergone surgery (other than microdiscectomy / laminectomy) at the same or adjacent level. 4. Subject has received conservative (non-surgical) treatment for back pain for a minimum of 6 months and is unresponsive. 5. Subject understands the conditions of enrollment and is willing to sign and date the Informed Consent. 6. Subject agrees to comply with visit schedule and completing study questionnaires. Exclusion criteria: 1. Subject has significant instability of the spine, e.g. isthmic spondolylisthesis or degenerative spondylolisthesis greater than grade 1. 2. Subject has degenerative disorder that requires TLIF at more than 2 levels between L2 and S1. 3. Subject has previously undergone lumbar spine surgery (other than microdiscectomy / laminectomy) at the same or adjacent level. 4. Subject is younger than 18 years of age, or older than 70 years of age. 5. Subject has a BMI of 40 or greater. 6. Subject has a history of metabolic bone disease as defined by any of the following: a. Subject is currently taking prescription medications that increase bone-mineral density (e.g Fosamax®, Didronel®, Forteo®, Zometa®). b. Subject was previously diagnosed with a metabolic bone disease (e.g. lumbar Paget's disease, osteoporosis or osteomalacia) c. Subject has a history of bone fractures suggesting bone disease. d. Subject has any other metabolic bone disease to a degree that lumbar spine instrumentation would be contraindicated. 7. Subject is osteoporotic. Subject is taking any of the following medications: a. Chronic oral or IV corticosteroid therapy (this is not intended to exclude inhalation medication for asthma) b. Medications known to potentially interfere with bone/soft tissue healing (e.g. methotrexate). c. Prescription medications that increase bone-mineral density (e.g Fosamax®, Didronel®, Forteo®, Zometa®). 8. Subject has diabetes mellitus requiring daily insulin management.

	9. Subject has any of the following: a. Progressive neuromuscular disease; OR b. Rheumatoid arthritis or other autoimmune disease; OR c. Active malignancy within the last 15 years (unless the malignancy was treated with curative intent and there have been no clinical signs or symptoms for at least 5 years); OR d. Active hepatitis; OR e. AIDS, ARC, or is HIV positive; OR f. Syringomyelia at any spinal level; OR g. Any other condition that would interfere with the subject self –assessment of pain, function or quality of life. 10. Subject has allergy to implant materials (titanium, titanium alloy). 11. Subject has active systemic infection or infection localized to the site of implantation. 12. Subject has primary or metastatic tumors involving the spine. 13. Subject has open wounds or inadequate issue tissue coverage over the operative site. 14. Subject has a history of significant mental illness or mental incapacity. 15. Subject is pregnant or interested in becoming pregnant in the next 3 years. 16. Subject is currently participating in another investigational study for a similar purpose. 17. Subject belongs to a vulnerable population (e.g., prisoner, severe drug abuser, developmentally disabled) that would compromise ability to provide informed consent or compliance with follow-up requirements. 18. Subject is currently a smoker, and will not cease smoking from the time of clinical trial enrollment up through 3 months post-operatively, nicotine users (cigarettes, patch, gum, etc.) for whom post-operative bone stimulation would be prescribed, or has a recent history of alcohol or other substance abuse within the past 2 years. 19. Subject is receiving workers compensation.
Study Device	Required Components: • Stryker AccuLIF TL Interbody Cages and associated instrumentation • Stryker supplemental fixation and associated instruments • Autogenous bone and/or allogenic bone graft comprised of cancellous or corticocancellous allograft chips.
Reference Therapy	TLIF with static cage

Ancillary Devices	The AccuLIF system is indicated for use with autogenous bone and/or allograft (cancellous or corticocancellous allograft chips) and supplemental fixation. Stryker supplementation fixation (Xia or ES2 pedicle screws must be used as part of the study protocol).
Statistical Methodology	All continuous data will be summarized using continuous descriptive statistics: number of subjects with responses (n), mean, standard deviation, median, minimum, and maximum. Changes from baseline, where appropriate, will be calculated as the follow-up measure minus the baseline measure, where baseline is defined as the last measure prior to the AccuLIF spinal system surgical procedure. All categorical data will be summarized using counts and percentages. Denominators for percentages will be the number of subjects in the respective patient population with nonmissing data. For the primary endpoint of an increase of 3 degrees or more of segmental lordosis, a one-sided analysis (alpha=0.05) will be used to assess significance. A one-sample t-test will be employed. Although the primary analysis will be at 24 months, similar analyses will be performed at each visit. Both the change from baseline and the results at each visit will be summarized. For all other radiographic parameters, the change from baseline will be analyzed at each visit using two-sided, one-sample t-tests (alpha=0.05) comparing the change from baseline to 0. Secondary and exploratory endpoints will be analyzed where appropriate. Where changes from baseline can be calculated for numerical data, statistical analyses will be performed. Analyses will follow the two-sided approach taken for the primary analyses. Data that is ordinal in nature, such as the changes in clinical outcomes, may be analyzed using Wilcoxon signed rank tests, comparing baseline measures to follow-up measures. All analyses will be two-sided and evaluated at an alpha level of 0.05.

Evaluation Schedule

Evaluation	Preop	Peri-op	6 weeks (± 2 wks)	3 months (± 1 mo)	6 months (± 1 mo)	1 year (± 2 mos)	2 years (± 2 mos)
Inclusion/ Exclusion	X						
Demographics & Medical History	X						
Preoperative Functional Evaluation	X						
Surgical Details		X					
SF-12	X		X	X	X	X	X
Post- operative Functional Evaluation			X	X	X	X	X
VAS (back and leg)	X		X	X	X	X	X
ODI	X		X	X	X	X	X
AP/Lateral	X		X	X	X	X	X
Flexion/Extension	X					X	X
Long standing Lateral	X					X	
MRI	X						
CT (fusion analysis)						X	X*

* Month 24 CTs are only expected for subjects that did not have a successful fusion at Month 12. All Month 24 CT collected will be analyzed.

1 Introduction

This document is a protocol for a human research study. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Standards, associated Federal regulations and all applicable research requirements.

1.1 Background

An estimated 80% of the US population will experience some form of back pain in their lifetime [(2)]. A number of treatment options are available to patients, based on age, presence of symptoms, and type of diagnosis. Chronic back pain associated with degenerative lumbar disease is a common symptom and tends to increase in severity with aging. In patients with prolonged, severe symptoms and/or instability, lumbar spondylotic disease, disc degeneration or herniation, facet degeneration, spondylolisthesis, stenosis, or scoliosis, lumbar fusion has been shown to be both clinically and cost effective [(2), (10)]. The objectives of fusion surgery of the lumbar spine include maintenance of coronal and sagittal balance, relief of pain, and solid arthodesis. Several surgical approaches to interbody fusion have been developed such as anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), lateral lumbar interbody fusion (LLIF) and transforaminal interbody fusion (TLIF). Each of these approaches has demonstrated high success rates, but each also comes with its own advantages and disadvantages.

Harms and Jezensky have been credited with development of the TLIF technique [(5)]. The technique involves a partial facetectomy followed by unilateral discectomy and decortication of the endplates. An interbody implant packed with bone is inserted into the disc space via the transforaminal approach and tapped into place. The posterior disc space may also be packed with bone. Reported advantages of this technique include little retraction of the nerve root and thecal sac while yielding the benefits of circumferential fusion and maintaining or regaining lumbar lordosis [(9)].TLIFs can be performed through an open, less invasive or minimally invasive technique.

Advances in this technique have also been driven by innovations to spinal fusion implants and grafting options, which have led to improvements in the rates of successful fusions. Since Bagby invented the first cage device in 1988 [(1)], numerous types of implants made from metal, carbon fiber composites, or titanium, have been designed and used in clinical cases [(12)].The implantation of interbody cages are imperative in the restoration of disc height and deformity correction in addition to restoring sagittal alignment. Recently, expandable interbody implants have been developed and introduced to the market. Features of this new technology include implants with short starting heights allowing surgeons to enter a collapsed disc space and then expanding the device in-situ, which could limit the impaction forces and overall destructive forces on the endplate. Although there is limited data on this novel technology, a few articles demonstrate that use of an expandable interbody fusion cage leads to good clinical results similar to static interbody cages such as achieving a solid bony fusion, improving a patient's quality of

life / pain assessment, and resulting in fewer mechanical device failures [3], [4], [5], [6], [11], [13], [16], [17]. Moreover, due to the dynamic technology of the expandable cages, some articles identify that greater improvements in vertebral disc space height and segmental lordosis can be achieved, all of which were accomplished without having to excessively drill, taper, or hammer instrumentation into the disc space in order to provide adequate distraction to access the vertebral space [7], [13], [16]. Greater improvements in disc height and segmental lordosis have been identified as clinically important outcomes to pursue because the recovery and maintenance of these measures affects the load bearing on the surgical site after operation, functions of the paraspinal muscles, and energy consumption during gait [8]. Moreover, restoration of lordosis has been noted as a significant factor when it comes to the occurrence of adjacent-level disease and symptomatic deformities, such as flat-back syndrome [14], [15], [18]. Expandable interbody cages offer a unique solution to restoring sagittal alignment without compromising or sacrificing the integrity of the vertebral structures.

While several expandable technologies exist for interbody cages, many alternatives are still in the early stages of development and have not been thoroughly investigated to identify the benefits and/or harms associated with this technique and instrumentation. The purpose of this study is to fully evaluate the clinical and radiographic outcomes of the AccuLIF expandable TLIF cage as a means to achieving a solid arthrodesis and improved clinical outcomes while also restoring disc height, improving segmental lordosis, and maintaining sagittal balance.

1.2 Investigational Device

The AccuLIF System was designed to provide access and treatment to the lumbar spine via a transforaminal approach. The AccuLIF expandable lumbar interbody technology offers surgeon users the ability to insert an interbody device at a smaller starting height, place the device in the desired position within the disc space, and then expand the device to the desired height based on patient anatomy to ensure endplate-to-endplate fit. The small starting height of the implant is designed to help preserve endplate structural integrity, minimize impaction forces during insertion, help reduce nerve root retraction on insertion and during expansion, and help to reduce the potential for neural injury during insertion of the implant.

1.3 Pre-Clinical Data

Pre-clinical testing has been conducted in support of the AccuLIF system.
The AccuLIF spacers have been tested according to ASTM and applicable standards. The AccuLIF spacers have been found to be substantially equivalent by US FDA via the 510(k) submission process.

1.4 Clinical Data to Date

This is the first, Stryker sponsored prospective clinical outcomes study of the AccuLIF System.

2 Study Objectives

2.1 Primary

The primary objective of this study to compare pre-operative and postoperative radiographic outcomes of a cohort treated for lumbar degenerative disease at one or two levels implanted with the AccuLIF spinal system at one level via TLIF procedure with supplemental fixation.
Primary Radiographic parameters are defined as:

- Disc height (anterior, middle, posterior in millimeters)
- Foraminal height (in millimeters)
- Segmental lordosis (at each TLIF level in degrees)
- Regional Lordosis: (inferior endplate T12-S1 in degrees)
- Sagittal balance: (C7-S1 in millimeters)

- Primary success is defined as an increase of 3 degrees or more of segmental lordosis post operatively.

It is hypothesized that patients implanted with the AccuLIF expandable TLIF cage will show restoration of anterior, middle, and posterior disc height, improve segmental lordosis and maintain regional and global sagittal balance post operatively.

Primary success is defined as an increase of 3 degrees or more of segmental lordosis post operatively.

It is also hypothesized that patients implanted with the AccuLIF expandable TLIF cage will show improvement in post-operative clinical outcomes when compared to pre-operative clinical status.

2.2 Secondary

The secondary objectives of the study are:

- To observe surgical parameters of the AccuLIF cohort.
  Defined as; operative time, estimated blood loss and length of stay.

- To assess the occurrence of neurologic complications by comparing pre-operative and postoperative neurologic evaluation.

- To assess clinical outcomes by comparing pre and post-operative patient measured outcomes defined as VAS, ODI and quality of life (QOL) as measured by SF-12 of the AccuLIF cohort.

- To observe the occurrence and frequency of additional complications of the AccuLIF cohort, including infection and nonunion.

- To observe standard radiographic outcomes defined as; fusion status, cage placement, migration / subsidence and parameters of supplemental fixation hardware including screw placement and subsidence.

2.3 Exploratory

The exploratory objectives of the study are:

- To evaluate the percentage of subjects that achieve > 3° lordosis and no negative changes in regional lordosis and global sagittal balance

- To compare changes in disc height, lordosis, sagittal balance as categorized by disc morphology. Disc morphologies are defined as:
  - **Tall and lordotic** Average Disc Height ≥11 mm **AND** Disc Angle >12°.
  - **Moderate** Average Disc Height ≥7 mm to ≤10 mm **AND** Disc Angle ≥5° to ≤12°.
  - **Flat and compressed:** Average Disc Height 0 mm to ≤6 mm **AND** Disc Angle 0° to <5°.

- To compare summary AccuLIF data to published literature of comparable TLIF outcomes.

3 Clinical Study Plan

3.1 Study Design

This is a prospective, post-market, multi-center, clinical evaluation of the AccuLIF system in patients requiring arthrodesis for degenerative disc disease (DDD) which may also include up to Grade I spondylolisthesis or retrolisthesis at one or two levels between L2 and S1. DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies.

3.2 Number of Centers

Up to 10 centers will participate in the trial.

3.3 Number of Subjects

Approximately 100 subjects will be enrolled in this study.

3.4 Estimated Study Duration

The enrollment period is approximately 9 months. The anticipated duration of this trial is approximately 36 months from the time the first patient is consented to the time the last patient is seen for his or her 24 month follow-up visit.

4 Subject Eligibility

4.1 Inclusion Criteria

All of the following inclusion criteria must be met.

1. Subject is skeletally mature and between 18 and 70 years of age.
2. Subject has one or more of the following diagnoses:
   DDD and up to Grade I spondylolisthesis or retrolisthesis, requiring decompression and arthrodesis at one or two contiguous levels between L2 and S1 as confirmed by CT, MRI, myelography and/or lateral flexion/extension films.
3. Subject has not previously undergone surgery (other than microdiscectomy / laminectomy) at the same or adjacent level.
4. Subject has received conservative (non-surgical) treatment for back pain for a minimum of 6 months and is unresponsive.
5. Subject understands the conditions of enrollment and is willing to sign and date the Informed Consent.
6. Subject agrees to comply with visit schedule and completing study questionnaires.

4.2 Exclusion Criteria

Patients may not be enrolled in the study if any of the following exclusion criteria are present.

1. Subject has significant instability of the spine, e.g. isthmic spondolylisthesis or degenerative spondylolisthesis greater than grade 1.
2. Subject has degenerative disorder that requires TLIF at more than 2 levels between L2 and S1.
3. Subject has previously undergone lumbar spine surgery (other than microdiscectomy / laminectomy) at the same or adjacent level.
4. Subject is younger than 18 years of age, or older than 70 years of age.
5. Subject has a BMI of 40 or greater.
6. Subject has a history of metabolic bone disease as defined by any of the following:
   a. Subject is currently taking prescription medications that increase bone-mineral density (e.g Fosamax®, Didronel®, Forteo®, Zometa®).
   b. Subject was previously diagnosed with a metabolic bone disease (e.g. lumbar Paget's disease, osteoporosis or osteomalacia)
   c. Subject has a history of bone fractures suggesting bone disease.

7. Subject has any other metabolic bone disease to a degree that lumbar spine instrumentation would be contraindicated. Subject is osteoporotic. Subject is taking any of the following medications:
    a. Chronic oral or IV corticosteroid therapy (this is not intended to exclude inhalation medication for asthma)
    b. Medications known to potentially interfere with bone/soft tissue healing (e.g. methotrexate).
    c. Prescription medications that increase bone-mineral density (e.g. Fosamax®, Didronel®, Forteo®, Zometa®).
8. Subject has diabetes mellitus requiring daily insulin management.

9. Subject has any of the following:
    a. Progressive neuromuscular disease; OR
    b. Rheumatoid arthritis or other autoimmune disease; OR
    c. Active malignancy within the last 15 years (unless the malignancy was treated with curative intent and there have been no clinical signs or symptoms for at least 5 years); OR
    d. Active hepatitis; OR
    e. AIDS, ARC, or is HIV positive; OR
    f. Syringomyelia at any spinal level; OR
    g. Any other condition that would interfere with the subject self –assessment of pain, function or quality of life.
10. Subject has allergy to implant materials (titanium, titanium alloy).
11. Subject has active systemic infection or infection localized to the site of implantation.
12. Subject has primary or metastatic tumors involving the spine.
13. Subject has open wounds or inadequate issue tissue coverage over the operative site.
14. Subject has a history of significant mental illness or mental incapacity.
15. Subject is pregnant or interested in becoming pregnant in the next 3 years.
16. Subject is currently participating in another investigational study for a similar purpose.
17. Subject belongs to a vulnerable population (e.g., prisoner, severe drug abuser, developmentally disabled) that would compromise ability to provide informed consent or compliance with follow-up requirements.
18. Subject is currently a smoker, and will not cease smoking from the time of clinical trial enrollment up through 3 months post-operatively; nicotine users (cigarettes, patch, gum, etc.) for whom post-operative bone stimulation would be prescribed, or has a recent history of alcohol or other substance abuse within the past 2 years.
19. Subject is receiving workers compensation.

5 Subject Enrollment

5.1 Treatment Assignment

All subjects will be assigned to receive lumbar interbody fusion via a TLIF approach with the AccuLIF TL implant with supplemental fixation via Xia or ES2 pedicle screws and bone graft from autograph and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone chips.

5.2 Randomization

This trial will not include randomization; all subjects will receive the same treatment.

6 Device Description

6.1 Study Device

The AccuLIF system was launched by Stryker Spine in 2014. AccuLIF is a comprehensive system of instruments and implants, including spacers comprised of titanium alloy, stainless steel and silicone rubber, with different size and height offerings. The AccuLIF expandable lumbar interbody technology offers surgeon users the ability to insert an interbody device at a smaller starting height, place the device in the desired position within the disc space, and then expand the device to the desired height based on patient anatomy to ensure endplate-to-endplate fit.
The patented expansion mechanism utilizes hydraulic pressure to expand the implant in 1mm increments to fill the disc space. The hydraulic expansion mechanism provides tactile and visual feedback during expansion and the mechanical lock offers confirmation that the implant is locked. The small starting height of the implant is designed to help preserve endplate structural integrity, minimize impaction forces during insertion, help reduce nerve root retraction on insertion and during expansion, and help to reduce the potential for neural injury during insertion of the implant. This procedure is done via a transforaminal lumbar interbody fusion, (TLIF) technique and can be performed as an open, MIS or LIS procedure. In an open or minimally invasive TLIF approach, the interbody space is generally accessed from a posterior approach, and an AccuLIF TL implant is inserted into the disc space after discectomy and endplate preparation.

6.2 Control Device

No control cohort will be enrolled as part of this study.

6.3 Ancillary Devices

The AccuLIF system is indicated for use with supplemental fixation. Stryker supplementation fixation in this study will include either Xia or ES2 systems. The AccuLIF TL cage is indicated for use with autogenous bone and/or allogenic bone graft comprised of cancellous and/or corticocancellous chips. See Appendix X for product instructions for use.

7 Study Evaluations

7.1 Pre-operative Visit

During the preoperative (first) visit, inclusion/exclusion criteria will be assessed. After eligibility has been confirmed by the site and the Sponsor, the subject's demographics and medical history

will be recorded, preoperative functional evaluation will be completed; neurological status (reflex, sensory, motor; and subject's current pain medications will be documented; SF-12 (Q of L), VAS (back and leg), and ODI(function) will be collected; and AP/Lateral, Flexion/Extension and long standing lateral radiographs and an MRI/CT (to confirm diagnosis) will be taken.

7.2 Peri-operative Visit

During the peri-operative visit, the patient will undergo lumbar interbody fusion via the transforaminal approach with the AccuLIF Expandable Interbody Fusion Cage with supplemental fixation in the form of pedicle screws. Surgical details will be collected including: estimated blood loss (EBL), operative times including skin-to-skin and anesthesia time, implant and screw sizes, and any intraoperative complications will be collected at time of surgery. The length of hospital stay will be recorded upon discharge. Any adverse events occurring during surgery through discharge will be collected and reported.

7.3 6 Week Visit

During the 6 week visit (42 days after surgery $\pm$ 2 weeks, study days 28 – 56), SF-12, VAS (back and leg), ODI and patient satisfaction will be collected; neurological status (reflex, sensory, motor); subject's current pain medication, work status, and smoking status will be assessed. AP/Lateral radiographs will be taken.

7.4 3 Month Visit

During the 3 month visit (90 days after surgery $\pm$ 2 weeks, study days 76 – 104), SF-12, VAS (back and leg), ODI and patient satisfaction will be collected; neurological status (reflex, sensory, motor); subject's current pain medication, work status, and smoking status will be assessed. AP/Lateral radiographs will be taken.

7.5 6 Month Visit

During the 6 month visit (180 days after surgery $\pm$ 4 weeks, study days 152 – 208), SF-12, VAS (back and leg), ODI and patient satisfaction will be collected; neurological status (reflex, sensory, motor); subject's current pain medication, work status, and smoking status will be assessed. AP/Lateral radiographs will be taken.

7.6 12 Month Visit

During the 12 month visit (365 days after surgery $\pm$ 8 weeks, study days 309 – 421), SF-12, VAS (back and leg), ODI and patient satisfaction will be collected; neurological status (reflex, sensory, motor); subject's current pain medication, work status, and smoking status will be

assessed. AP/Lateral and Flexion/Extension radiographs, and long standing lateral will be taken. CT scan to assess bony fusion, will be taken as well.

7.7 24 Month Visit

During the 24 month visit 24 months (730 days after surgery ± 8 weeks, study days 674 – 786), SF-12, VAS (back and leg), ODI and patient satisfaction will be collected; neurological status (reflex, sensory, motor); subject's current pain medication, work status, and smoking status will be assessed. AP/Lateral and Flexion/Extension radiographs will be taken. For subjects that did not have a successful fusion at Month 12, a 24 month CT scan will be taken to re-assess fusion.

8 Adverse Events

8.1 Reporting of Adverse Events

8.1.1 General Physical Examination Findings

At screening for inclusion into the study, any clinically significant abnormality should be recorded as a preexisting condition and reported on the History and Physical CRF. From the time of consent forward, any new clinically significant findings or abnormalities that meet the definition of a protocol defined AE must also be recorded and documented as an AE. AEs which are reportable under this protocol include those that related to the device, the index procedure, the lumbar spine and those that meet the definition of serious.

8.1.2 Adverse Event Reporting Period

The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. The start of study procedures is considered to be the point of consent. Any AEs which fit the protocol defined reportable events must be reported from the time of consent until study completion.

At each contact with the subject the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on protocol defined AEs should be recorded immediately in the source document and also in the appropriate AE module of the CRF. All clearly related signs, symptoms and abnormal diagnostic procedure results should be recorded in the source document and grouped under one diagnosis, as appropriate. The clinical course of each event should be followed until resolution or until it is determined at the end of the study that the AE will not resolve.

8.2 Adverse Event Definitions

Following is a list of general AE definitions.

Adverse Event

An **AE** is any untoward medical occurrence in a clinical investigation subject, which changes the medical baseline of the subject. An AE can be an unfavorable and unintended sign, symptom or disease, whether or not related to the study device (AEs may also be referred to as complications). See Section 8.1, Reporting of Adverse Events, for the AE reporting requirements for this study.

Anticipated Adverse Event

An **anticipated AE** is an AE, of which the nature, severity or degree of incidence is known and identified in applicable product labeling, published literature or the study protocol. The list of anticipated events is provided in Section 12, Risk/Benefit Assessment.

Serious Adverse Event

A **SAE** meets one or more of the following definitions:

- Resulted in in-patient hospitalization
- Resulted in prolonged existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Resulted in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Was a life-threatening situation
- Resulted in patient death

Adverse Device Effect

An **adverse device effect** (ADE) is a negative change in the subject's health that may have been caused by, or associated with, the use of the device.

Unanticipated Adverse Device Effect

An **unanticipated adverse device effect** (UADE) is any serious adverse effect on health, safety or any life-threatening problem or death caused by, or associated with, a device if that effect is a problem or death not previously identified in nature, severity or degree of incidence, or any other unanticipated serious problem associated with a device and related to the rights, safety or welfare of subjects.

8.3 Adverse Event Notification to Study Sponsor

8.3.1 Notification to Ethics Committee/Institutional Review Board by Investigator

Reports of AEs (including follow-up information) must be submitted to the IRB according to their specific requirements. Copies of each report and documentation of IRB notification and receipt will be kept with the investigator's study files.

8.4 Recording of Adverse Events

All protocol defined AEs occurring during the study period must be recorded; this includes events that occur between scheduled visits. The clinical course of each event should be followed until resolution or stabilization.

8.5 Surgical Interventions

Surgical interventions are classified separately from adverse events. All surgical interventions (defined below) must be recorded on the appropriate eCRF within five (5) business days and reported to Stryker Spine within forty-eight (48) hours.

Surgical interventions are defined as follows.

Revision - a procedure that adjusts or in any way modifies or removes **part** of the original implant configuration, with or without replacement of a component of the original configuration. This may include adjusting the position of the original configuration.

Removal - a procedure in which *all* of the original implant components are removed, with or without replacement.

Supplemental Fixation - a procedure in which additional instrumentation that is not part of the original configuration under study is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system).

Reoperation - any surgical procedure at the treated level that does not remove, modify, or add any components to the implant configuration (e.g., repair of dural leak). Reoperations unrelated to the spinal implants (e.g., treatment for wound infection, or surgical decompression for pre-existing leg (radicular) pain) are recorded as surgical interventions, but are not considered individual subject failures.

Any device removed during the course of the study is required to be returned to Stryker Spine for analysis.

8.6 Medical Monitoring

It is the responsibility of the investigator to oversee the safety of the study at his/her center. This safety monitoring will include careful assessment and appropriate reporting of AEs, as previously noted. Stryker will conduct formal investigations via the Product Surveillance Department of those AEs which are submitted through our Product Inquiry System.

9 Statistical Plan

9.1 Efficacy Parameters

9.1.1 Primary Objective Parameters

The primary objective parameters of this study are the change in pre-operative to post-operative radiographic outcomes of a cohort treated for degenerative disease at one or two levels implanted with the AccuLIF spinal system at one level via TLIF procedure with supplemental fixation. The primary objective will be evaluated at 12 months post-operatively.
Primary Radiographic parameters are defined as:

- Disc height (anterior, middle, posterior in millimeters)
- Foraminal height (in millimeters)
- Segmental lordosis (at each TLIF level in degrees)
- Regional Lordosis: (inferior endplate T12-S1 in degrees)
- Sagittal balance: (C7-S1 in millimeters)

- Success is defined as an increase of 3 degrees or more of segmental lordosis 12 months post operatively.

9.1.2 Primary Objective Hypothesis

Success is defined as an increase of 3 degrees or more of segmental lordosis post operatively. The primary null hypothesis is as follows:

H_0: Subjects implanted with the AccuLIF spinal system will have less than 3 degrees increase in segmental lordosis 12 months post-operatively.

H_0: Subjects implanted with the AccuLIF spinal system will have an increase of at least 3 degrees in segmental lordosis 12 months post-operatively.

9.1.3 Primary Objective Analysis

For the primary endpoint of an increase of 3 degrees or more of segmental lordosis, a one-sided analysis (alpha=0.05) will be used to assess significance. A one-sample t-test will be employed. Although the primary analysis will be at 12 months, similar analyses will be performed at each visit. Both the change from baseline and the results at each visit will be summarized.

For all other radiographic parameters, the change from baseline will be analyzed at each visit using two-sided, one-sample t-tests (alpha=0.05) comparing the change from baseline to 0.

9.1.4 Secondary Objective Parameters

The secondary parameters of the study, evaluated at each study visit, are as follows:

- Surgical parameters of the AccuLIF cohort, including operative time, estimated blood loss and length of stay.
- The occurrence of neurologic complications, defined as abnormal changes from the pre-operative to post-operative neurologic evaluations.
- Changes in clinical outcomes, comparing pre- and post-operative patient measured outcomes defined as VAS, ODI and quality of life (QOL) as measured by SF-12.
- The occurrence and frequency of additional complications of the AccuLIF cohort, including infection and nonunion.
- Standard radiographic outcomes defined as; fusion status, cage placement, migration / subsidence and parameters of supplemental fixation hardware including screw placement and subsidence.

9.1.5 Secondary Objective Analysis

Where changes from baseline can be calculated for numerical data, statistical analyses will be performed. Analyses will follow the two-sided approach taken for the primary analyses. Data that is ordinal in nature, such as the changes in clinical outcomes, may be analyzed using Wilcoxon signed rank tests, comparing baseline measures to follow-up measures. All analyses will be two-sided and evaluated at an alpha level of 0.05.

9.1.6 Exploratory Objective Parameters

The exploratory parameters of the study, evaluated at each study visit, are as follows:

- The percentage of subjects that achieve > 3° increase in lordosis and have no negative changes in regional lordosis and global sagittal balance
- Changes in disc height, lordosis, and sagittal balance as categorized by disc morphology. Disc morphologies are defined as:
  - **Tall and lordotic** Average Disc Height ≥11 mm **AND** Disc Angle >12°.

- **Moderate** Average Disc Height ≥7 mm to ≤10 mm **AND** Disc Angle ≥5° to ≤12°.
- **Flat and compressed:** Average Disc Height 0 mm to ≤6 mm **AND** Disc Angle 0° to <5°.

- The differences in AccuLIF data compared to published literature of comparable TLIF outcomes. The published literature sources will be identified in a formal statistical analysis plan.

9.1.7 Exploratory Objective Analysis

Exploratory analyses will be performed using the same methodology as the secondary analyses.

9.2 Safety Parameters

9.2.1 Safety Parameters

Safety parameters will include adverse events, AEs, unanticipated AEs, ADEs, and UADEs.

9.2.2 Safety Analysis

Safety data will be summarized descriptively, using descriptive statistics and/or counts and percentages. Statistical analyses will not be performed on safety data.

9.3 Missing Data

The primary analyses will be based on observed data. In addition, sensitivity analyses will be performed including missing data using a Markov Chain Monte Carlo multiple imputation method and using the last observation carried forward.

9.4 Statistical Methodology

9.4.1 Data Summary

All continuous data will be summarized using continuous descriptive statistics: number of subjects with responses (n), mean, standard deviation, median, minimum, and maximum. Changes from baseline, where appropriate, will be calculated as the follow-up measure minus the baseline measure, where baseline is defined as the last measure prior to the AccuLIF spinal system surgical procedure.

9.4.2 Sample Size Calculation

Sample size calculations are based on the primary analysis of the change from baseline in segmental lordosis at 12 months, utilizing a one-sided, one-sample t-test. Based on previous experience it is assumed that the true change in segmental lordosis after 12 months will be 5 degrees. It is also determined that a change of at least 3 degrees is considered clinically meaningful. With a standard deviation of up to 6 degrees and assuming 90% power, 79 subjects are required to show a difference of at least 3 degrees. Assuming a dropout rate of up 20%, 100 subjects will be enrolled.

9.4.3 Interim Analysis and Early Stopping Considerations

There are no planned interim analyses.

9.5 Efficacy Patient Population

All patients enrolled in the study with any follow-up efficacy assessment (radiographic assessment) will be included in the efficacy patient population.

9.6 Safety Patient Population

All patients who undergo the surgical procedure (lumbar interbody fusion via the transforaminal approach with the AccuLIF Expandable Interbody Fusion Cage with internal supplemental fixation in the form of pedicle screws) will be included in the safety patient population.

10 Study Procedures

10.1 Subject Recruitment and Screening

Patients will be recruited at the study centers during preoperative visits through normal referral patterns. All patients recruited for this study will have the capacity to give informed consent. Advertising for the study at each center will be at the discretion of the investigator. All handouts, brochures, advertisements, etc. must be approved by the IRB/EC prior to the dissemination of any recruitment materials to potential subjects.

10.2 Patient Informed Consent and Guidelines

All patients for this study will be provided an Informed Patient Consent Form describing this study and providing sufficient information for them to make an informed decision about their participation. The Informed Patient Consent Form must contain all elements required by the FDA under 21 CFR Part 50, in addition to any other elements required by state, local and institutional policies. See Appendix E for a copy of the Model Informed Patient Consent. This will be submitted with the protocol for review and approval by the IRB for the study. All patients must provide written consent after having had adequate time to consider their participation in the study. The formal consent of a patient, using the IRB approved Informed

Patient Consent Form, must be obtained before that patient is submitted to any protocol related procedures that are not part of normal care. Written documentation of consent must be provided on the Informed Patient Consent Form's signature page in addition to a note in the patient medical records indicating the date that consent was obtained. The investigator-designated research professional obtaining the consent must also sign this Informed Patient Consent Form. The patient or his/her legal representative should receive a signed copy of the Informed Patient Consent Form, according to GCP guidelines.

The procedure for obtaining informed consent is outlined below:

- Use a current IRB approved copy of the Informed Patient Consent Form.
- Review thoroughly with the patient before having them sign.
- After the patient has consented to the procedures, ensure he/she signs and dates the Informed Patient Consent Form.
- The person obtaining consent also signs and dates the signature page.
- Provide a copy of the Informed Patient Consent Form to the patient.
- If required, provide the hospital with a copy of the signed Informed Patient Consent Form.
- Maintain the signed original in the patient's study chart.

10.3 Early Withdrawal of Subjects

When and How to Withdraw Subjects

In the event that the subject is discontinued by the investigative center prior to the final study evaluation, the subject will be notified by the center that he/she is no longer in the study and a Study Termination CRF will be completed.

The following is a list of reasons for which subjects may be withdrawn and the date of termination that should be used on the Study Termination CRF in each situation. This list is not all inclusive:

Termination Reason	**Date of Termination**
Death	Date of death
Investigative center termination	Date of study close-out visit
Lost to follow-up	Date Stryker termination approval given
Voluntary withdrawal	Date subject notified center of withdrawal
Removal of study device	Date of removal procedure
Study device not implanted	Date of surgery
Surgery not performed	Date Stryker termination approval given

At the time of study surgery it is required that the following components are implanted: AccuLIF interbody implant, supplemental fixation via pedicle screws, bone graft (autogenous and / or corticocancellous allograft chips).

Revision or removal of the AccuLIF Cage System constitutes a failure and study termination for the subject.

If revision of supplemental fixation is required during the study, the event is considered a reoperation and does not constitute a failure or study termination.

If the subject fails to return for his/her follow-up appointments, every effort should be made to contact the subject to assess his/her health status. If, after attempting to contact the subject through three documented phone calls and a certified letter, the subject still does not respond, he/she will be considered lost to follow-up. A Study Termination CRF will be completed **only after notifying Stryker of the subject's status** and **being given approval to terminate**.

In the event a subject does not have surgery, Stryker should be contacted to discuss if/when the surgery will be rescheduled. If the surgery is rescheduled more than 4 months from the date of preoperative data collection, the subject will need to be re-consented, all preoperative data will need to be re-collected and all original preoperative data will need to be removed from the database. If the surgery is not to be rescheduled or if the subject is no longer considered an appropriate study candidate, a Study Termination CRF may be completed **only after notifying Stryker of the subject's status** and **being given approval to terminate**.

When a subject completes the study according to protocol, including the final study evaluation, a Study Termination CRF will be completed.

11 Data Management

11.1 Database

For this project, the Sponsor will utilize an Electronic Data Capture (EDC) system which is securely hosted on the Internet through a "cloud." This EDC system is 21 CFR Part 11 compliant and additionally supports CDISC, HIPAA, and GCP. Study sites will be trained on the use of the EDC system prior to study commencement at each center.

11.2 Confidentiality

This study will comply with the 2002 HIPAA privacy rule. As such, Stryker will only collect that information which is necessary to support the objectives of the clinical study. Stryker will take precautions to ensure that data received is as de-identified as possible. In the case that some identified information is received, Stryker will ensure that any identifying information is not reported. Study subjects will authorize Stryker to use their health information in support of the clinical study during the informed consent process. Should a subject choose to withdraw authorization, Stryker may use data collected prior to the withdrawal of authorization in order to maintain data integrity.

11.3 Source Documents

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, study worksheets, laboratory notes, memoranda, subject questionnaires, pharmacy dispensing records, recorded data from automated instruments, radiographs, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

All data points collected during follow-up visits must be documented in the subject's chart. This includes neurologic assessment, pain and function as well as AEs and additional comments. The informed consent process should also be documented in the patient chart. Monitors, defined further in Section 13, will be comparing the CRFs against source documents for adequacy. The monitors will seek to draw a reference between each data point on the CRF and the subject's chart. Thus, one cannot derive pain, neurologic status or function based on a chart note that reads "Patient doing well." Every effort should be made to ensure complete source documentation.
Centers are required to create a source documentation plan including any applicable source documentation worksheets prior to enrollment.

11.4 Case Report Forms

All CRF data will be entered in the electronic CRF database provided by the Sponsor's electronic data capture (EDC) system. All sites are expected to enter data into the EDC system within 5 business days of each data collection visit. The EDC system can easily be accessed using the current versions of all the major browsers (Internet Explorer, Safari, Firefox, Chrome, etc.) All sites will receive training and access to the EDC system as part of the site initiation visit. Subject completed questionnaires will be administered on paper CRFs and entered into the database by the study site.

11.5 Data Clarifications

Data queries may appear in the EDC system during data entry, may be entered into the system by data management, or may be sent to the site directly during monitoring visits and other reviews by the Sponsor staff. All data queries, regardless of modality, must be responded to within 5 days from the date the query is entered.

11.6 Protocol Deviations

Any deviation from this protocol will be reported to Stryker as well as to the EC/IRB according to their reporting procedures. Protocol Deviations for this study include, but are not limited to, the following:

- Informed consent deviations, including but not limited to:

- Study procedures performed prior to informed consent
- Incorrect informed consent version used
- Patient enrolled does not meet the inclusion/exclusion criteria
- Protocol specified study component(s) not implanted
- Visit deviations, including:
- Unavailable primary endpoint
- One or more required eCRFs/ images (radiographs/CTs) not done
- Evaluations occurred outside of protocol specified time window
- Radiographs / CT not evaluable
- Missed visit

If the center anticipates a possible protocol deviation, the investigator or SC should contact Stryker for guidance.

11.7 Records Retention

It is the investigator's responsibility to retain study essential documents for 2 years after the date of the final report, or in the case of non-compliance, 2 years after the date of investigative center termination. These documents should be retained for a longer period if required by an agreement with Stryker.

12 Risk Benefit Assessment

12.1 Risk Category

There are no additional risks associated with participating in this study over and above that of the transforaminal lumbar interbody fusion procedure.

12.2 Potential Risk

The study involves the routine assessment of a lumbar interbody fusion procedure. The AccuLIF System has been cleared for use by the FDA and will be used according to its labeling, included in Appendix C. Assessment involves questionnaires, patient and physician assessments as well as routine imaging (such as radiographs, MRI and / or CT scans). The information collected will be kept confidential and will comply with the HIPAA privacy rule.

While the expected life of lumbar fusion components is difficult to estimate, it is finite. These components are made of foreign materials, which are placed within the body for the potential restoration of mobility or reduction of pain. However, due to the many biological, mechanical and physiochemical factors which affect these devices but cannot be evaluated in vivo, the components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone. Patients involved in an occupation or activity that applies excessive loading upon the implant (e.g., substantial walking, running, lifting, or muscle strain) may be at risk for failure of the fusion and/or device. The procedure will not restore function to the level expected with a normal, healthy spine, and the patient should not have unrealistic functional expectations.

12.3 Expected Complications

A number of complications and adverse events may be anticipated during the course of the study. Many of these are a consequence of general surgical procedures. The more common serious possible risks and/or complications associated with general surgery are:

- Superficial or deep-set infection
- Pneumonia
- Clots (emboli) in the blood vessels or lungs
- Brusing or blood loss (hemorrhage)
- Reactions to the drugs or anesthetic agents used during and after surgery
- Scar tissue and/or heterotopic bone formation
- Inflammatory phenomena
- Nerve damage, numbness, weakness, sensory / motor loss
- Systemic infection, including urinary tract infection
- Change in mental status
- Phlebitis (painful and swollen veins)
- Post-surgical muscle or tissue pain and swelling at the incision
- Possible need for blood products
- Hyperthermia or hypothermia
- Pneumonia
- Decrease in bone density due to stress shielding
- Failure of the tissue to heal properly, wound infection, or wound dehiscence
- Reactions to transfused blood
- Injury to the spine during intubation
- In rare situations, blindness, cardiac arrhythmia, hypotension, heart attack, paralysis, stroke, or death.

Additional anticipated adverse events associated with the subject's surgery are included in the treating institution's standard consent form for surgery.

Since the AccuLIF Expandable Interbody Fusion Cage is implanted using a posterior /transforaminal approach some of its potential complications are specific to the method of entry (2, 3). The following risks are associated with the posterior / transforaminal surgical approach:

- Injury to nerves;
- Injury to blood vessels (arteries and veins) leading to bruising (hematoma) and swelling;
- Neurological and spinal dura mater lesions from surgical trauma;
- Neurological problems secondary to blood vessel injury such as cerebral ischemia, stroke, or gastrointestinal and/or genital side effects;
- Shortness of breath or breathing discomfort following removal of breathing tube;
- Injury to the lumbar plexus;
- Injury to the dura;
- Temporary or permanent loss of bowel or bladder function;
- Potential complication of pain from the incision in the hip to harvest bone; should it be taken;
- Pseudoarthrosis and failure to form visible bridging trabecular bone;
- Hemorrhage (blood loss);
- Post-surgical muscle and tissue pain;
- Injury to other parts of the spine, such as pedicles and transverse processes that may result in temporary or permanent pain or other neurologic symptoms;
- A solid fusion may put more stress on the disc above or below the fusion, which may lead to other complications over time, such as: loss of proper spinal curvature, abnormal motion, disc degeneration, and pain;
- Cessation of growth of the fused portion of the spine;
- Regional Pain Syndrome (sympatheic nerve response) resulting in burning pain, or other abnormal sensation usually usually in the upper extremities. These include, but are not limited to: autonomic dysfunction, reflexive sympathetic dystrophy, or Homer's Syndrome.

It is anticipated that the adverse events associated with the AccuLIF implant will be similar to those of other spinal implants. Specifically, the AccuLIF implant may:

- loosen, break, or move (migrate) with respect to the other

bones of the spine;

- fail to expand within the interbody space (becomes a static cage);
- move or dislodge from the spine (partially or completely), causing injury to nearby organs and tissues in the lower back including blood vessels, nerve roots, spinal cord, dural sac
- fracture the endplate portion of the vertebra, subside, or dislodge a bone fragment during implantation or over time
- Surgical instruments used in the procedure may break, resulting in loose fragments of instrument material, (which is not implantable grade) in the body. Removal of these fragments may cause damage to bones and/or soft tissues. Non-removal of these fragments may cause adverse allergic reactions or injury to sensitive nearby organs.
- Cause adverse / allergic reactions to implant materials (titanium, stainless steel, cobalt-chromium-molybdenum and silicone rubber).
- The bank bone (for the interbody spacer) may transmit infection
- not be positioned properly in the spine, and not maintain proper spinal curvature
- fracture or perforation of the bones of the spine or dislodge bone fragments that may result in temporary or permanent pain or other neurologic symptoms, or surgery;
- cause adverse reactions (titanium)
- collapse at any point post-operatively;
- require another surgery to correct the problem;
- require another surgery to correct improper placement of the device;
- The donor bone (for the interbody spacer) may transmit infection
- fail to fuse (from bridging bone) the bones of the spine as intended
- put more stress on the disc above or below the fusion, which may lead to other complications over time, such as: loss of proper spinal curvature, abnormal motion, adjacent disc degeneration, and pain
- cause adverse reactions due to wear debris; or
- not reduce the pain or disability associated with DDD.

12.4 Protection Against Risk

Subjects will be treated in the best medical judgment of the investigator, regardless of the study protocol. If an investigator must deviate from the written protocol to protect the health or well-being of the subject, this deviation will be promptly reported to both the IRB and Stryker.

12.5 Potential Benefits to Subject

There is no guarantee that subjects will personally benefit from inclusion in this study. Subjects may undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance. This study seeks to provide clinicians information about this system/device by comparing this treatment/device to published results for other treatments/devices. Information gathered in this study may benefit others undergoing this procedure in the future.

13 Monitoring, Auditing and Inspecting

13.1 Study Monitoring Plan

Monitors are persons employed by sponsors to review the conduct of clinical studies to assure that the clinical investigators abide by their obligations to conduct clinical studies properly. Proper monitoring ensures adequate protection of the rights of human subjects, the safety of subjects involved in a clinical investigation and the quality and integrity of data submitted as a result of the investigation.

This study will be monitored at least once per year, with additional visits, as necessary. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study-related facilities and has adequate space to conduct the monitoring visit. The monitor will review all source documents and compare them to the data contained in the CRFs, in addition to performing a periodic review of regulatory documents such as IRB approvals. The monitors will need the following when they visit:

- An area where they can review study data
- Subject case books
- Patient charts pulled at the center
- Regulatory documents
- Time to meet with the SC and the investigator

13.2 Auditing and Inspecting

A quality assurance audit is a form of review that provides additional confidence to the sponsor concerning the validity and accuracy of clinical study data that must be submitted to the FDA or for publication. The purpose of investigator audits is to ensure that the investigator has

maintained all study information according to the sponsor's protocol and standard operating procedures and in compliance with FDA regulations.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, Stryker and/or government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities.

14 Ethical Considerations

This study is to be conducted according to United States standards of GCPs and applicable government regulations including 21 CFR Parts 50 and 56 as well as 45 CFR Parts 160 and 164.

This protocol and any amendments will be submitted to a properly constituted independent EC/IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Stryker before commencement of this study. The investigator may be asked to provide a list of EC/IRB members and their affiliates to Stryker, if available.

All patients considered for this study will be provided an Informed Patient Consent Form describing this study and providing sufficient information for patients to make an informed decision about their participation. This Informed Patient Consent Form must be modified to contain center specific information and submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a patient, using the EC/IRB approved Informed Patient Consent Form, must be obtained before that patient is submitted to any study procedure. This Informed Patient Consent Form must be signed by the patient or legally acceptable surrogate and the investigator-designated research professional obtaining the consent.

15 Study Finances

15.1 Funding Source

This study is financed by Stryker Spine.

15.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (e.g. patent ownership, royalties or financial gain greater than the maximum allowable by their institution) must have the conflict reviewed by their EC/IRB or a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by Stryker prior to participation in this study.

15.3 Subject Stipends or Payments

There is no compensation to subjects for participation in this study. However, subject attrition can occur for a variety of reasons, including a subject's loss of health insurance coverage. In a case where a patient has lost health insurance coverage and no other coverage is available, Stryker may, on a case-by-case basis, reimburse investigators for office visits and radiographic charges for subjects involved in this study in order to facilitate data retrieval. The physician or the office staff should contact the CSM prior to scheduling the subject to discuss this possibility and receive pre-approval. After CRFs are completed, the physician must submit either evidence of coverage denial (e.g. explanation of benefits) or a letter explaining that the subject does not have insurance. Other visits, procedures and assessments done other than those specified in the protocol will not be reimbursed. Reimbursement may be provided under the following conditions:
Study subjects lose insurance coverage after enrollment into the study.
An insurance carrier refuses to pay for a follow-up visit and/or radiographs.
An insurance carrier refuses to provide subject referral to see the investigator for follow-up.

Under extreme circumstances, and with prior approval, Stryker my reimburse a subject for the cost of transportation to and from the investigator's office for a protocol-required office visit.

This policy is the same for all participating subjects and does not bias against any particular subject or cohort.

16 Publication Plan

It is anticipated that publication of the multi-center study results will be compiled and submitted to a peer-reviewed journal at the time the study cohort reaches 6 weeks, 1 and 2 years of follow-up. Additional publication proposals may be made by investigators at any time and will be considered.

This study will utilize the guidelines for authorship published by the International Committee of Medical Journal Editors (ICMJE). This guidance can be referenced at www.icmje.org.

Publications will be facilitated by the Chair and the primary investigator (PI) of the study. Both individuals will be chosen by Stryker.

The PI is solely focused on the multi-center publications and progress towards those publications, including recurring updates to centers, center motivation as well as authorship. If the PI does not produce a draft of a publication within 90 days of receiving the results data, Stryker will delegate the responsibility to other investigators in the study at its discretion.

The Chair reviews all additional publications proposed by participating investigators based upon the study results prior to study completion, on an ongoing basis. This review includes whether or not a proposal will be pursued, as well as imposition of guidelines as to publication completion and criteria.

The following summarizes the possible roles of these parallel positions:

Chair	**PI**
-Contributes to study design -Assists with study questions requiring expert clinical opinion -Assists with identification of investigators -Reviews additional publication proposals submitted by investigators -Contributing author, if ICMJE guidelines met	-Contributes to study design -Assists with study questions requiring expert clinical opinion -Assists with identification of investigators and maintains performance -Updates investigators on progress towards multi-center results -Primary author, multi-center publication of primary endpoint data

At the completion of the study, each participating study investigator shall have independent publication privileges for his/her own center's results. These manuscripts and abstracts will be delayed until after the 6 week, 1 and 2-year multi-center publications are submitted.

All publications of the data shall be submitted to Stryker for review prior to submission for publication. Stryker shall not edit or otherwise influence the publications other than to ensure that confidential information is not disclosed, that no off-label use of Stryker devices is promoted and that the data is accurately represented. Any publications resulting from this study must be submitted to Stryker for review at least 60 days prior to submission of publication.

17 References

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