

**POST APPROVAL STUDY PROTOCOL
FOR THE
TWO LEVEL
SIMPLIFY®
CERVICAL ARTIFICIAL DISC**

SPONSOR:

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JUNE 14, 2021

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PROTOCOL SIGNATURE PAGE

POST APPROVAL STUDY PROTOCOL
FOR THE
TWO LEVEL
SIMPLIFY® CERVICAL ARTIFICIAL DISC

Version June 14, 2021

I have read the contents of this protocol. I agree to conduct the study according to the protocol and the procedures described.

Study Site Number: _____

Investigator Signature and Date: _____

Investigator Printed Name: _____

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1. NAME AND ADDRESS OF SPONSOR AND REPRESENTATIVES**1.1 STUDY SPONSOR**

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[REDACTED]

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[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

2. STUDY PLAN

2.1 NAME AND INTENDED USE OF THE DEVICE

Device Classification & Generic Name: Class III; Total Disc Replacement

Device Trade Name: Simplify® Cervical Artificial Disc

Indication: Simplify® Cervical Artificial Disc is indicated for use in skeletally mature patients for reconstruction of the disc at one or two levels from C3-C7 following discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to abnormality localized to the disc space and manifested by at least one of the following conditions confirmed by radiographic imaging (e.g., X-rays, computed tomography (CT), magnetic resonance imaging (MRI)): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. Patients receiving Simplify® Cervical Artificial Disc should have failed at least six weeks of non-operative treatment or demonstrated progressive signs or symptoms despite nonoperative treatment prior to implantation. Simplify® Cervical Artificial Disc is implanted via an open anterior approach.

2.2 PURPOSE OF STUDY

This study is intended to demonstrate the 5-year long-term safety and efficacy of the Simplify® Cervical Artificial Disc (“Simplify Disc”) in subjects enrolled in the non-randomized two-level Simplify Disc IDE study. This study was conducted under IDE G150206.

2.2.1 DESCRIPTION OF DEVICE

The Simplify Disc is a cervical artificial disc manufactured from PEEK endplates and a mobile, zirconia-toughened alumina ceramic core. The PEEK endplates have a plasma-sprayed titanium coating. The articulating surfaces on the endplates have a concave surface and the core has two convex surfaces.

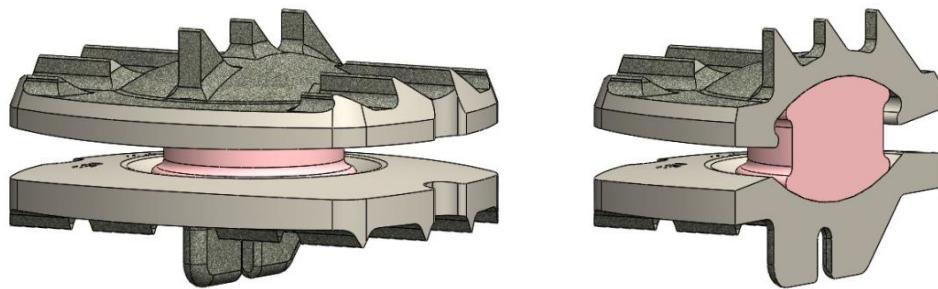


Figure 1. Representative Image of Simplify Disc

For the Simplify Disc family, two core options (i.e., either small or large) are used for all assemblies. The articulating features of superior and inferior endplates are identical and congruent with the appropriate core. Superior and inferior endplates are available in three footprints, three thicknesses, and two lordosis angles. The superior endplates have a retention ring feature. All endplates are titanium coated on the bone interfacing surfaces, with two options available for coating thickness. All endplate components, regardless of configuration, have identical manufacturing process flow, including packaging and sterilization.

The Simplify Disc is designed to provide a theoretical maximum of $\pm 12^\circ$ in any combination of flexion-extension and lateral bending, unlimited axial rotation, and 1-2 mm translation. This range is intended to permit the patient's anatomy to determine actual range of motion without imposing an artificial limit that may be restrictive to the patient's kinematic profile. The maximum range of motion *in vivo* will be dictated by the patient's anatomical boundaries or the device limits, whichever is smaller.

2.3 PROTOCOL STUDY CONDUCT

2.3.1 STUDY OBJECTIVE

The objective of this clinical study is to evaluate the 5 year long-term safety and effectiveness of the two-level Simplify Disc compared to conventional anterior cervical discectomy and fusion (“ACDF”) in skeletally mature patients for reconstruction of two contiguous discs from C3 to C7 following discectomy at two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces that are unresponsive to conservative management.

2.3.2 STUDY HYPOTHESIS

The study hypothesis is that in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces at two contiguous discs levels from C3 to C7 that are unresponsive to conservative management, the Month 60 composite clinical success (CCS) rate of the Simplify Disc will be no worse than conventional ACDF. Individual success for Simplify Disc and the historical control ACDF is defined as follows:

- Neck Disability Index (NDI) score improvement of at least 15 points from pre-operative;
- Maintenance or improvement in neurological status;
- No serious adverse event classified as implant associated or implant/surgical procedure associated; and
- No additional surgical procedure classified as a “failure.”

2.3.3 STUDY DESCRIPTION

This is a prospective, multi-center post-approval study (PAS) evaluating subjects in the non-randomized two level Simplify Disc IDE study compared to ACDF subjects in a non-concurrent historical control [REDACTED]. The historical control population will only include the subjects who were selected using a PS model developed in the two level Simplify Disc IDE study and reviewed by FDA in the approved PMA to establish comparability between the study populations.

2.3.4 STUDY POPULATION

This will include up to 170 subjects eligible for study enrollment from sixteen (16) sites in the two level Simplify Disc IDE study who consent to long-term follow-up. Additionally, up to 17 training subjects from the two level Simplify Disc IDE study from seventeen (17) sites will be enrolled. Up to 151 historical ACDF control subjects will be included in the PAS population. The final number of included ACDF subjects is not yet known as CEC adjudications are on going of the post month 24 data.

2.3.4.1 INCLUSION CRITERIA

All subjects enrolled in the two level Simplify Disc IDE study are considered for this long-term follow-up study.

2.3.4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

- Subjects who were not implanted with the Simplify Disc during the IDE study
- Subjects who had a secondary surgical intervention at the index level during the IDE study
- Subjects who were withdrawn or withdrew consent to participate in the IDE study
- Subjects who do not consent to participate in long-term follow-up post-approval study

2.3.5 STUDY DESIGN

2.3.5.1 OVERALL STUDY DESIGN

This is a prospective, multi-center post-approval study to evaluate the 5-year long term safety and effectiveness of the Simplify Disc at two levels. The historical control population will only include the fusion subjects who were selected using a PS model developed in the two level Simplify Disc IDE study and approved PMA. The Simplify Disc data from the training subjects will be summarized separately and not used in the primary comparison to control. Study subjects will be evaluated annually (\pm 2 months for the 36-month visit and \pm 3 months for the 48- and 60-month visits) for components of the primary endpoint, secondary study endpoints and safety up through 5-year post-implantation. Fusion (control) subjects were not evaluated at the 48-month visit. Primary study success will be evaluated at the 5-year timepoint.

2.3.6 STUDY PROCEDURES

2.3.6.1 INFORMED CONSENT

Only patients who sign Informed Consent for participation in PAS will be allowed to participate in this clinical study. Subjects who do not speak English must be provided a copy of an IRB approved consent in their native language, or (if the process is approved by the site's IRB) an IRB acceptable translator. The original signed consent will be retained in each subject's study file.

2.3.6.2 STUDY EVALUATIONS, PROCEDURES AND ASSESSMENTS

Follow-up evaluations annually at Month 36, Month 48, and Month 60 will include:

- AP and lateral X-rays (plain films);
- Flexion-extension X-rays (used to determine range of motion);
- Lateral bending films (Simplify Disc only);

- Radiographic core lab evaluations;
- Postoperative subject survey (medication and satisfaction)
- Dysphagia Handicap Index (Simplify Disc only);
- NDI assessment;
- SF-36 Health Survey;
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);
- Foraminal compression test;
- Physician perception of results;
- Neurologic evaluation;
- Gait assessment;
- Study related medications (Simplify Disc only);
- Work status;
- Treatment satisfaction assessment and
- Adverse events as defined by Section 2.3.8 of this protocol.
- [REDACTED]

Neurologic status will be evaluated by a qualified evaluator, who may be an MD, DO, an RN or a PA. The neurologic evaluation will include a motor and sensory assessment and reflex responses. Reflexes that are hypo-reflexic will be considered as normal. Gait abnormality will be assessed. For the purposes of this clinical study, only medication taken for neck/arm pain including the class of medication, i.e. non-narcotic, narcotic (strong and weak), and muscle relaxant, will be collected postoperatively.

All radiographic endpoints will be evaluated independently by one core laboratory.

2.3.6.2.1 Radiographic Assessments

The following radiographic assessments will be made by two independent musculoskeletal radiologists at the core lab. A third independent radiographic reviewer will adjudicate in instances of disagreement. The radiographic assessments will include:

- Intervertebral Angle;
- Change in Intervertebral Angle;

- Horizontal Translational;
- Change in Horizontal Translational;
- Global Range of Motion;
- Change in Global Range of Motion;
- Disc Height (assessed by determining Functional Spinal Unit [FSU] height and by directly measuring height of disc space)
- Change in Disc Height;
- Disc Angle;
- Change in Disc Angle;
- Spondylolisthesis;
- Change in Spondylolisthesis;
- Device Condition;
- Device Bending;
- Device Breaking;
- Device Fracture;
- Device Subsidence (can also be derived with FSU Height);
- Device Migration;
- Device Protrusion;
- Radiolucency;
- Heterotopic Ossification;
- Bridging Bone;
- Maintenance of PreOp Motion;
- Osteophyte Formation;
- Endplate Sclerosis;
- Kellgren-Lawrence Adjacent Level Disc Degeneration;
- Additional Observations.

2.3.6.2.2 [REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.3.6.2.3 Study Completion, Termination or Loss to Follow-up

SimpliY Disc subjects are expected to remain in the study until the 60 months post implantation assessment. The study completion/ termination evaluation will be made at the 60 months assessment, or at earlier time point if the subject withdraws or is withdrawn from the study.

Subjects may be withdrawn from a clinical study early due to withdrawal of Informed Consent, loss to follow-up, or Investigator medical decision. Any premature termination from the study will be documented, including the primary reason for withdrawal. In the event of a secondary index surgery requiring removal of a spinal system, every effort will be made to retrieve the explanted device for analysis. The instructions for the surgical technique for device removal of the Simplify Disc are included in the Study Manuals. Any subjects with a device removal of the Simplify Disc or who have any other secondary index surgery will be discontinued from the study after the next follow-up study visit.

2.3.7 STATISTICAL CONSIDERATIONS

2.3.7.1 PRIMARY ENDPOINT

The study hypothesis is that in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces at two contiguous levels from C3 to C7 that is unresponsive to conservative management, the Month 60 composite clinical success (CCS) rate of the Simplify Disc will be no worse than conventional ACDF when success of ACDF is evaluated at Month 60. Individual success for Simplify Disc and the historical control ACDF is defined as follows:

- Neck Disability Index (NDI) score improvement of at least 15 points from pre-operative;
- Maintenance or improvement in neurological status¹;
- No serious adverse event classified as implant associated or implant/surgical procedure associated; and
- No additional surgical procedure classified as a “failure.”

Overall success will be determined based on data collected during the 36 months to 60 months of follow-up. Each element of the neurological study exam will be evaluated for maintenance or improvement.

All secondary index surgeries will be classified as failures.

Per FDA Guidance for the Preparation of IDEs for Spinal Systems, the following definitions apply for the PAS:

- Reoperation - any surgical procedure at the index level(s) that *does not involve* modification, addition or removal of any components of the device and is not considered a removal, revision, or supplemental fixation.

1 Maintenance or improvement in neurological status will be based on motor, sensory, and myelopathic gait assessments.

- Revision – any procedure in the postoperative or follow-up period that adjusts or in any way modifies either one or both of the original implant configurations (e.g., adjusting the position of the original configuration, removal with replacement with same type of study implant).
- Removal – a procedure that removes one or more components of the original implant configuration without replacement with the same type of trial implant.
- Supplemental fixation – a procedure at the index level(s) in which additional spinal devices not approved as part of the protocol are placed.

Other – any additional surgical procedure not classified as a removal, revision, supplemental fixation, or reoperation.

2.3.7.2 STUDY SUCCESS

The null hypothesis is that the probability of achieving Month 60 composite clinical success (CCS) for patients implanted with the Simplify Disc device at two levels is no more than 0.10 smaller than the probability of ACDF control patients achieving Month 60 CCS. This study will be considered a success if the PS-quintile adjusted, multiple imputation based, 1-sided p-value for rejecting this null hypothesis is less than or equal to 0.05.

2.3.7.3 DESIGN OF THE OBSERVATIONAL STUDY

Two hundred (200) subjects were enrolled in the two level Simplify Disc IDE population. Of these, 18 Simplify Disc subjects were training subjects. The historical ACDF control population included █ subjects. The █ available subjects (182 Simplify Disc (excluding training subjects) and █ historical ACDF control) were assessed via the Propensity Score (PS) sub-classification process. After applying an established heuristic for 3 iterations (6 models), a total of 182 Simplify Disc and 170 historical ACDF control subjects were retained in the final PS designed sample. Analysis of subject demographic and baseline data showed no meaningful differences between the treatment groups. The PS-selected population and PS sub classes defined in the IDE study G150206 will be utilized for the purposes of this study. Per the exclusion criteria, additional subjects are not enrolled into the PAS due to reasons that preclude long-term Simplify Disc data collection (e.g., SSI).

2.3.7.4 JUSTIFICATION OF CONTROL AND EXPERIMENTAL GROUP SUCCESS RATES

Based on multiple imputation and including N=182 Simplify Disc subjects and N=170 historical controls, the Month 24 PS adjusted success rates were estimated to be 86.7% and 77.1%, respectively,

for a group difference of 9.6% (90% LB CI 2.1%). The lower bound of the 90% 2-sided CI is equivalent to the lower bound of the 95% 1-sided non-inferiority CI. In the completer's analysis set, 153 of 173 Simplify Disc subjects achieved Month 24 overall success, and 105 of 145 Controls achieved Month 24 overall success.

2.3.7.5 SAMPLE SIZE ANALYSIS

For the purposes of sample size calculation, it is estimated that 85% of the estimated 170 Simplify Disc subjects (N=145) who are not terminal failures or lost to follow-up will be available at year 5. It is estimated that 70% of the estimated 151 (N=106) Control subjects who are not terminal failures (defined as SSI or Intra-op deviation) or died, will be available at year 5. This calculation reviewed the available NDI scores at month 60 among the 151 subjects who were not known to already be not included. It is expected that this number will be not be exact due to on going safety adjudication by the CEC.

Based on these results, it was conservatively estimated that the 5-year overall success rates would be 70% of the observed rates, that is, 62% and 54% for Simplify Disc and historical ACDF control, respectively. If the success rates in both groups are larger, statistical power will be larger and so this power analysis would be conservative. With sample sizes of 145 and 106 and assuming 62% and 54% success, the power to detect non-inferiority is 89% at a one-sided 0.05 significance level.

2.3.7.6 SUPERIORITY TESTING

If the non-inferiority study success criterion is met, superiority testing will be performed in the primary analysis set. It will be concluded that the Simplify Disc is superior to the ACDF control if the PS-quintile adjusted one-sided p-value determined from the multiple imputation is less than 0.05.

2.3.7.7 ADDRESSING MISSING PRIMARY OUTCOME DATA

Because of the availability of subject level data in controls that correspond to the subject level data to be collected in the prospective study, missing data will be addressed in the same fashion to how missing data would have been addressed in a randomized clinical trial. Multiple imputation will be used to impute missing final NDI in patients otherwise evaluable for primary CCS. For each of 20 imputed data sets, the primary PS stratified device group difference will be made resulting in a standard error for each. The final device group difference will be the average of the multiple imputed datasets and its standard error will account for both within (usual) and between imputation error.

In addition to multiple imputation, sensitivity analysis will be provided based on tipping point analyses. These are analyses in which all possible combinations of successes and failures are assumed for patients missing primary CCS and the fraction of scenarios in which the statistical conclusion changes is summarized. Best case and worst case, all missing success, and all missing failures scenarios will also be summarized.

2.3.7.8 ANALYSIS OF SECONDARY ENDPOINTS AND ADVERSE EVENTS

Secondary effectiveness endpoints will be compared between groups over time using PS-adjusted group differences and 95% PS-adjusted confidence intervals for group differences. Should the number of events be too small or zero for one group, the undjusted group specific rate will only be provided as was done in the 2-level PMA. Adverse events will be summarized by event counts and per subject incidence rates for categories of AE, for specific AEs, by relationship to device and procedure, and for SAEs. Counts will also be summarized by time of onset category and by AE severity. Where applicable, AE summary tables will include 95% confidence intervals for group differences in incidence rates.

For each study group and for important subgroups separately, the primary outcome (i.e., patient success) and secondary endpoints, as well as the incidence of specific complications, will be tabulated and presented by follow-up interval. Comprehensive tables will provide frequency and percentage distributions and descriptive statistics as appropriate in total and for each study group separately.

Survival analysis methods will be used to describe time to event outcomes including time to secondary surgical intervention.

2.3.7.8.1 Secondary Endpoints

Secondary endpoints include:

- Clinically significant improvement in one or more radicular symptoms or myelopathy at each annual timepoint compared to baseline in the IDE study for the two level Simplify Disc and for the historical control ACDF. The data collected will reflect the number of patients who improved (numbers will be stratified to reflect clinical improvement), who remain unchanged, and who deteriorated at each study time point. These endpoints will be graded and defined as follows:
 - Pain questionnaires will be used to evaluate each of the following pain locations:

- Neck pain
- Arm pain
- Left arm pain (investigational group only);
- Right arm pain (investigational group only);
- Motor status - A change of one or more grade levels in muscle strength will be regarded as clinically significant.
- Sensory status - Sensation will be graded as normal or abnormal (diminished or absent). Any changes from abnormal to normal or absent to diminished will be regarded as clinically significant improvement.².
- Time to recovery defined as the earliest time at which a minimum 15-point (out of 100) NDI improvement is reached.
- Disc height at each annual timepoint compared to baseline (6 weeks) in the IDE study for the two level Simplify Disc. Both levels had to be a disc height success to claim success for overall disc height. Disc height success for each level is based on either the anterior or posterior measurements meet the following criterions:
 - Post-operative Height – 6 Week Post-operative Height \geq -2 mm
- Adjacent level deterioration at each annual timepoint compared to baseline in the investigational group of the IDE study for the two level Simplify Disc.
- Displacement or migration of the device for the investigational group; only changes of $>$ 3 mm will be considered significant due to the margin of error in radiographic determination of displacement distances.
- Return to work status post-operatively.
- Patient satisfaction and perceived effect at each annual timepoint. Success for each satisfaction question (three) will be defined as either a “Definitely True” or “Mostly True” response. Success for the perceived effect will be defined as either a “Completely Recovered,” “Much Improved,” or “Slightly Improved” response.
- Health Survey (SF-36) at each annual timepoint compared to baseline. Success will be expressed in terms of the PCS (physical component summary) and MCS (mental component summary) scores and will be defined as a maintenance or improvement in status post-

² Hacker *et al.*, *supra* note 7, at 2648; Aids to the Investigation of Peripheral Nerve Injuries (UK Medical Research Council, War Memorandum No. 7 (2d ed. Rev. 1943).

operatively as compared to the pre-operative condition. To be classified as a success for each component summary, the following criteria must be met:

- PCSPostop - PCSPreop ≥ 0
- MCSPostop - MCSPreop ≥ 0
- Dysphagia Handicap Index (DHI scale) for the Simplify Disc at 60 months compared to baseline in the two level IDE study.
- Adjacent Level Motion (Stability) will be compared at 60 months to baseline.
- Results at 60 months will be categorized by the physician's perception of the subject's condition (excellent, good, fair, or poor).
- Gait assessment at 60 months compared to baseline. This will be based on Nurick's classification. Success will be defined as maintenance or improvement in the post-operative status as compared to the pre-operative condition:
 - Pre-operative Score – Post-operative Score ≥ 0

2.3.7.9

2.3.7.11 OTHER OUTCOMES

Radiographs will be used to monitor the occurrence of some of the above adverse events, including subsidence of the device into the adjacent disc or other changes in the implant, and spinal instability. In addition, at each visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator will elicit information concerning adverse events by asking standard questions. Adverse events considered unusual for the patient population (i.e., occurring with greater

frequency than anticipated or with greater severity than anticipated), key to safety or efficacy, or device related will require detailed reporting on the appropriate case report form.

2.3.8 SAFETY ASSESSMENT

2.3.8.1 ADVERSE EVENTS

An adverse event is defined as any clinically adverse sign, symptom, syndrome, or illness that occurs or worsens during the operative and postoperative periods of the trial, regardless of causality, that is not otherwise being measured in the trial. Adverse events, whether or not device related, must be reported on the appropriate case report form. . Any adverse event that occurred prior to treatment with the medical device will be documented in the patient's pre-operative medical history in the two level Simplify Disc study. Only adverse events which occurred in the Month 36 through Month 60 visits or are continuing from the two level Simplify Disc IDE study or are new or have worsened during the course of this study will be evaluated in the safety assessment.

Analysis of adverse events will be conducted using the methods specified in section 2.3.7.8.

2.3.8.2 SERIOUS ADVERSE EVENTS

2.3.8.2.1 Description

A Serious Adverse Event (SAE) is an adverse event which:

1. Led to a death,
2. Resulted in life threatening illness or injury,

NOTE: the term "life-threatening" refers to an event in which the patient was at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3. Resulted in subject hospitalization or prolongation of existing hospitalization,
4. Resulted in subject disability or permanent damage or required intervention to prevent permanent impairment/damage.

2.3.8.3 UNANTICIPATED ADVERSE DEVICE EFFECTS

2.3.8.3.1 Description

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this Protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

2.3.8.3.2 Reporting

Adverse event information will be collected on all subjects. At each subject encounter, the investigator will determine if there has been an AE since the last encounter and if any previous AE's are ongoing or have resolved. All adverse events must be reported on the Adverse Event Form.

If an Investigator is unsure about whether to report a finding as an adverse event, s/he should report the event on the AE form.

SAEs and UADEs must be reported to the Sponsor, as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event. SAEs and UADEs must also be reported to the approving IRB per the IRB's reporting requirements.

2.3.8.4 POTENTIAL RELATIONSHIP OF ADVERSE EVENTS

The CEC will be asked to assess the potential relationship of the adverse event to the implanted device and to the procedure and classify the causality of the event according to the following definitions.

- **Implant-associated:** An AE for which there is a reasonable possibility that the event may have been caused primarily by the implant(s).
- **Surgical procedure-associated:** An AE for which there is a reasonable possibility that the event may have been caused primarily by the surgical procedure.
- **Implant/Surgical procedure-associated:** An AE for which there is a reasonable possibility that the event may have been caused both by the implant(s) and surgical procedure.
- **Not Related:** An AE for which sufficient information exists to indicate that the etiology is unrelated to the implant(s) or surgical procedure.

- Undetermined: An AE for which sufficient information is not available at the time of the event to determine its causality.

2.3.8.5 ASSESSMENT OF SEVERITY

The CEC will use the following terms for assessment of severity:

- Mild (grade 1): The AE is noticeable to the patient, but does not interfere with routine activity. The AE does not require removal of the implant(s).
- Moderate (grade 2): The AE interferes with routine activities of the patient, but responds to symptomatic therapy or rest. The AE does not require removal of the implant(s).
- Severe (grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy and may require hospitalization. In addition, the AE may require removal of the implant(s).
- Life-Threatening (grade 4): The AE requires removal of the implant(s), or the patient is at immediate risk of death, even if not related to the implant(s).

2.3.8.6 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) will adjudicate all reported adverse events. This will include all SAEs, including secondary surgeries at the index and adjacent levels, primary endpoint failure, and neurologic deterioration.

The CEC may determine neurologic status has declined at 60 months compared to baseline based on changes including:

- Motor Assessment: shift from baseline.
- Sensory Examination: shift from normal to absent or impaired; impaired to absent.
- Myelopathic Gait Abnormality Class: any worsening.

The CEC will also review all UADEs. Adverse events will be classified by the CEC based on seriousness, relationship to device and procedure, and severity. The CEC will also adjudicate protocol deviations. The CEC will consist of three members with related expertise in spine surgery or neurosurgery, with the option for one position to be filled by a radiologist, who are not affiliated with the Sponsor or who are not participating in the study. The recommendations of the CEC and become part of the clinical trial data set.

2.4 RISK ANALYSIS

2.4.1 RISKS

No physical risks are anticipated as a result of participation in the long-term follow-up study. The amount of radiation exposure to subjects is relatively small.

Subjects may require additional surgery at the treated spinal level:

- Reoperation - any surgical procedure at the index level(s) that *does not involve* modification, addition or removal of any components of the device and is not considered a removal, revision, or supplemental fixation.
- Revision – any procedure in the postoperative or follow-up period that adjusts or in any way modifies either one or both of the original implant configurations (e.g., adjusting the position of the original configuration, removal with replacement with same type of study implant).
- Removal – a procedure that removes one or more components of the original implant configuration without replacement with the same type of trial implant.
- Supplemental fixation – a procedure at the index level(s) in which additional spinal devices not approved as part of the protocol are placed.
- Other – any additional surgical procedure not classified as a removal, revision, supplemental fixation, or reoperation.

Risks associated with the use of both the Simplify Disc and control spinal systems are expected to be comparable. All secondary index surgeries will be regarded as failures and reported accordingly.

2.5 STUDY MONITORING

2.5.1 MONITORING ORGANIZATION

Study monitoring functions, with assistance from the Sponsor or designee for any study training visits, will be performed by an independent clinical monitoring organization, in compliance with recognized Good Clinical Practices as applied to medical device studies, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. §812.46. The monitoring organization will act as the Clinical Monitor. The major function of the Clinical Monitor is to observe and assess the quality of the clinical study.

In addition to ensuring adequate communication between the investigators and the study Sponsor, the monitor's duties include on-site and remote visits and review of study documents and results. The monitoring organization has been provided with appropriate training regarding the Simplify Disc and will operate under written procedures to ensure compliance with the protocol.

2.5.2 MONITORING VISITS

Monitoring visits include a pre-study visit, periodic visits and a close-out visit at the end of the site's participation in the study. The pre-study visit, which may be performed by the Sponsor or designee, will be conducted remotely and is intended to provide an opportunity to review the Study Plan and associated study documents with the Investigator and to ensure that the Investigator has IRB approval and all required documentation prior to initiating the post approval study.

Periodic visits are intended to assess adherence to the Study Plan, maintenance of Records and Reports, and provides for review of source documents for accuracy, completeness, and legibility. During these periodic visits, the monitor is required to assess the progress of the study toward meeting study objectives; to identify any concerns that stem from observations of device performance and/or review of the subject records, study management documents or Informed Consent documents; to ensure that the site has assessed adverse events according to protocol requirements; and to ensure accountability of all subjects. A periodic visit may be performed on-site or remotely.

The monitor's final visit at completion of the study is intended to ensure that all the data have been properly completed and to have a closing meeting with the Investigator and his/her staff members to discuss findings, observed problems and potential solutions.

Reports of the monitoring visits will be made by the monitor and should include a means of tracking resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, a final report will be prepared by the monitor for each site.

2.5.3 DATA COLLECTION

Data will be compiled using an Electronic Data Capture system operated by the Independent Monitoring Organization. The Clinical Monitor will verify that appropriate data are recorded for all study subjects for whom Informed Consent is obtained; and that no study evaluations are completed without Informed Consent. Documentation will be provided for study subjects who choose to

terminate study participation and for subjects terminated by their physicians. A full explanation of the reasons for non-participation will be provided.

Data will be reviewed to identify inconsistent or missing data, SAEs, and UADEs. Data problems will be addressed in calls to the study sites and during site visits. Electronic Case Report Forms and data files will be secured to ensure confidentiality. Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications and adverse events are reported as required under Section 2.2.6.1 and Section 2.2.7 of this protocol.

2.5.4 REVIEW OF STUDY DOCUMENTS

The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. Although not limited to these, the following documents will be audited:

- The Clinical Trial (Investigator) Agreement signed by the investigator, indicating his/her agreement to participate in the investigation and willingness to comply with all study requirements.
- Electronic Case Report Forms will be reviewed for errors, omissions, internal consistency, and signature and dates in the appropriate sections. The monitor will assume responsibility for any follow-up activities that result from review of these forms. Subject Informed Consent documents will be reviewed for completeness.
- Study Monitor Reports by a site monitor will be reviewed by the senior monitor. The monitor will assume responsibility for any corrective action.

2.5.5 MEDICAL MONITORING

NuVasive has appointed a qualified spine surgeon to oversee all medical monitoring issues. Duties of the Medical Monitor include, but are not limited to:

- Being available to investigators for questions regarding adverse event reporting;
- Being available to the FDA for medically related questions regarding this clinical study;
- May attend CEC meetings as a NuVasive Official.

2.5.6 ROLE OF CO-PRINCIPAL INVESTIGATORS

NuVasive has appointed experienced spine surgeons to oversee all Co-Principal Investigator issues. Duties of the Co-Principal Investigators include, but are not limited to:

- Review the protocol;
- Being available to investigators for questions regarding protocol criteria and surgical related questions;
- Being available to the FDA for medically related questions regarding this clinical study.

2.5.7 DISPOSITION OF ANY EXPLANTED STUDY DEVICES AND DATA

Should it be necessary to explant the Simplify Disc, NuVasive shall provide surgical instructions in the Simplify Disc Surgical Technique Guide and a device retrieval kit and instructions detailing the appropriate procedure for handling explanted devices. All Simplify Disc explant procedures will attempt to collect tissues adjacent to the device (e.g., bone-implant interface) for independent histopathological and wear examination.

All information received by the study Sponsor or authorized agents of the study Sponsor pertaining to subjects will be held on a confidential basis. This information may be subject to audit by regulatory authorities where appropriate. Authorized agents of the study Sponsor will have the right to inspect and copy information in subject files. Copies will be blinded to replace subject identifying information with subject identifiers.

2.6 INFORMED CONSENT

Suitable candidates will be informed about the nature of the study and the possible risks involved, and will be provided the opportunity to sign Informed Consent. The subject will be able to ask questions of the investigator, and will be allowed to review the consent form at his/her leisure. The investigator or the study coordinator, as appropriate, may answer additional questions the subject may have at an additional office visit or by telephone. It is possible that the subject will sign the consent at home, and so the date of signature of the Investigator (if Investigator signature is required by IRB) may be different from the date of the subject's signature.

Only patients who sign Informed Consent will be allowed to participate in this clinical study. Subjects who do not speak English will be provided a copy of an IRB approved consent in their native language, or (if the process is approved by the site's IRB) an IRB acceptable translator.

The original of the site's IRB approved Informed Consent template will be kept in the site's study files. Each site will provide the study Sponsor with a copy of the IRB approved and stamped Informed Consent template. The original signed consent will be retained in each subject's study file.

2.7 INVESTIGATOR TRAINING, RESPONSIBILITIES AND OBLIGATIONS

2.7.1 INVESTIGATOR TRAINING

The sponsor will provide appropriate training to each investigator prior to study initiation.

Training will address topics including the study procedures

2.7.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that the investigation is conducted according to this protocol and following the Investigator Agreement. Prior to study participation, the Investigator is required per 21CFR54 to describe any financial arrangements they have with the study Sponsor, and this information is to be updated as appropriate. The Investigator is responsible for ensuring that Informed Consent is obtained from each study subject.