NCT04630626

POST APPROVAL STUDY PROTOCOL

for the

SIMPLIFY®

CERVICAL ARTIFICIAL DISC

SPONSOR:

NuVasive, Inc.
7475 Lusk Boulevard
San Diego,
CA 92121
Phone: 858-909-1800

JUNE 30, 2021

PROTOCOL SIGNATURE PAGE

POST APPROVAL STUDY PROTOCOL

for the

SIMPLIFY® CERVICAL ARTIFICIAL DISC

Version June 30, 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: _____

1. NAME AND ADDRESS OF SPONSOR AND REPRESENTATIVES 3

1.1 STUDY SPONSOR 3

1.2 [redacted] 3

1.3 [redacted] 4

1.4 [redacted] 4

2. STUDY PLAN 5

2.1 NAME AND INTENDED USE OF THE DEVICE 5

2.2 PURPOSE OF STUDY 5

2.2.1 Description of Device 5

2.3 PROTOCOL STUDY CONDUCT 6

2.3.1 Study Objective 6

2.3.2 Study Hypothesis 7

2.3.3 Study Description 7

2.3.4 Study Population 7

2.3.4.1 Inclusion Criteria 7

2.3.4.2 Exclusion Criteria 8

2.3.5 Study Design 8

2.3.5.1 Overall Study Design 8

2.3.6 Study Procedures 8

2.3.6.1 Informed Consent 8

2.3.6.2 Study Evaluations, Procedures and Assessments 9

2.3.7 Statistical Considerations 12

2.3.7.1 Primary Endpoint 12

2.3.7.2 Study Success 13

2.3.7.3 Design of the Observational Study 13

2.3.7.4 Justification of Control and Expirmental Group Success Rates 13

2.3.7.5 Sample Size Analysis 13

2.3.7.6 Superiority Testing 14

2.3.7.7 Addressing Missing Primary Outcome Data 14

2.3.7.8 Analysis of Secondary Endpoints and Adverse Events 15

2.3.7.9 [redacted] 16

2.3.7.10 [redacted] 17

2.3.7.11 Other Outcomes 17

2.3.8 Safety Assessment 18

2.3.8.1 Adverse Events 18

2.3.8.2 Serious Adverse Events 18

2.3.8.3 Unanticipated Adverse Device Effects 19

2.3.8.4 Potential Relationship of Adverse Events 19

2.3.8.5 Assessment of Severity 20
2.3.8.6 Clinical Events Committee 20
2.4 RISK ANALYSIS 21
2.4.1 Risks *21*
2.5 STUDY MONITORING 22
2.5.1 Monitoring Organization *22*
2.5.2 Monitoring Visits *22*
2.5.3 Data Collection *23*
2.5.4 Review of Study Documents *23*
2.5.5 Medical Monitoring *24*
2.5.6 Role of Co-Principal Investigators *24*
2.5.7 Disposition of any Explanted Study Devices and Data *24*
2.6 INFORMED CONSENT 24

1. NAME AND ADDRESS OF SPONSOR AND REPRESENTATIVES

1.1 STUDY SPONSOR

NuVasive, Inc.

7475 Lusk Boulevard

San Diego, 92121

Phone: 858-909-1800

[redacted]

1.2 [redacted]

[redacted]

1.3 [redacted]

[redacted]

1.4 [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 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 Simplify Disc IDE study. This study was conducted under IDE G140154.

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.

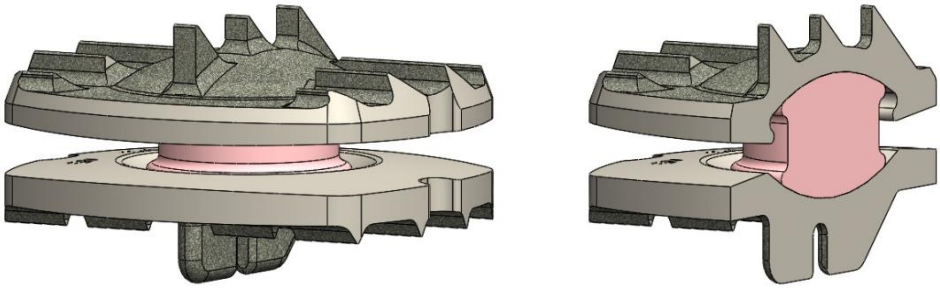

Figure 1. Representative Image of Simplify Disc

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 ± 12° 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 Simplify Disc compared to conventional anterior cervical discectomy and fusion ("ACDF") for treatment of intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain or myelopathy due to a single-level abnormality localized to the level of the disc space at one level from C3 to C7 that is 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 or without neck pain or myelopathy due to a single-level abnormality localized to the level of the disc space at one level 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. Individual success for Simplify Disc and the historical control ACDF is defined as follows:

- Improvement on the NDI of at least 15 percentage points compared to baseline (pre-op) in the Simplify Disc IDE study, and
- No device failures by Month 60, and
- No subsequent surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation) by Month 60.

2.3.3 STUDY DESCRIPTION

This is a prospective, multi-center post-approval study (PAS) evaluating subjects in the non-randomized Simplify Disc IDE study compared to ACDF subjects in a non-concurrent historical control Kineflex®|C Disc study. The historical control population will only include the subjects who were selected using a PS model developed in the 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 142 subjects eligible for study enrollment from fifteen (15) sites in the Simplify Disc IDE study who consent to long-term follow-up. Additionally, up to 13 training subjects from the Simplify Disc IDE study from thirteen (13) sites will be enrolled. Up to 106 historical ACDF control subjects will be included in the PAS population.

2.3.4.1 INCLUSION CRITERIA

All subjects enrolled in the 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. The historical control population will only include the fusion subjects who were selected using a PS model developed in the 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 (± 2 months) for components of the primary endpoint, secondary study endpoints and safety up through 5-year post-implantation. 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;
- Dysphagia Handicap Index (Simplify Disc only);
- NDI assessment;
- SF-12v2 Health Survey (Simplify Disc only);
- VAS pain assessments (neck and arm; neck, left arm and right arm (Simplify Disc only));
- Neurologic evaluation;
- Study related medication status (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, reflex responses and the determination of the presence or absence of dysphagia, dysphonia, clumsiness, foot drop, atrophy, cramping, muscle spasms, numbness and gait abnormality.

Muscle strength will be graded for the deltoid (C5), biceps (C6), and triceps (C7) according to a 6-point scale where 0 = no movement, 1 = trace of muscle contraction; 2 = active movement without gravity; 3 = active movement against gravity; 4 = active movement against gravity/resistance; and 5 = normal response.

Study related medication status will include only medications taken or administered for the following

- Pain (any type);
- Inflammation (any type);

- Muscle relaxation;
- Numbness &/or tingling;
- Hormonal replacement therapy and
- Other medications related to or given for the subject's spinal condition.

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:

- Angular Motion;
- Change in Angular Motion;
- Translational Motion;
- Change in Translational Motion;
- Global Range of Motion;
- Change in Global Range of Motion;
- Disc Height;
- Change in Disc Height;
- Disc Angle;
- Change in Disc Angle;
- Spondylolisthesis;
- Change in Spondylolisthesis;
- Bridging Bone;
- Fusion Status;
- Device Condition;
- Device Subsidence;
- Device Migration;
- Device Protrusion;
- Radiolucency;
- Heterotopic Ossification;

- Osteophyte Formation;
- Endplate Sclerosis;
- Adjacent Level Disc Degeneration;
- Change in ALDD and;
- Additional Observations.

2.3.6.2.2 [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 or without neck pain or myelopathy due to a single-level abnormality localized to the level of the disc space at one level from C3 to C7 that is unresponsive to conservative management or have the presence of progressive symptoms, 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:

- Improvement on the NDI of at least 15 percentage points compared to baseline in the Simplify Disc IDE study, and
- No device failures by Month 60, and
- No subsequent surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation) by Month 60.

Device failure is defined as breakage, migration, or mechanical failure of the components as defined in the Radiographic Evaluation Protocol. Failure of the allograft will not be counted as device failure in the historical ACDF control group.

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 that *does not involve* modification, addition or removal of any components of the device" in the postoperative or follow-up period.
- Revision - any procedure in the postoperative or follow-up period that adjusts modifies or removes part of the original implant configuration *with or without* replacement of a component – may include adjusting the position of the original configuration in the postoperative or follow-up period.
- Removal - a procedure where the entire device is removed with or without replacement of the device in the postoperative or follow-up period.

- Supplemental fixation – a procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement of a rod/ screw system).

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 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

One hundred sixty-six (166) subjects were enrolled in the Simplify Disc IDE population. Of these, 16 Simplify Disc subjects were training subjects. The historical ACDF control population included 133 subjects. The 283 available subjects (150 Simplify Disc (excluding training subjects) and 133 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 150 Simplify Disc and 117 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 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 Expirmental Group Success Rates

Based on multiple imputation and including N=150 Simplify Disc subjects and N=117 historical controls, the Month 24 PS adjusted success rates were estimated to be 93.0% and 73.6%, respectively, for a group difference of 19.4% (90% LB CI 10.9%). 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, 132 of 142 Simplify Disc subjects achieved Month 24 overall success, and 68 of 96 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 142 Simplify Disc subjects (N=121) who are not terminal failures or lost to follow-up by Month 24 will be available at year 5. It is estimated that 60% of the estimated 106 (N=64) Control subjects who are not terminal failures or lost to follow-up by Month 24 will be available at year 5.

Based on these results, it was conservatively estimated that the 5-year overall success rates would be 70% of the observed rates, that is, 65% and 50% 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 121 and 64, and assuming 65% and 50% success, the power to detect non-inferiority is 96% 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 group differences and 95% confidence intervals for group differences. 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. Tables and graphical displays will be provided for both the primary effectiveness and safety populations as appropriate.

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 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:
    - A visual analog scale (VAS) will be used to evaluate each of the following pain locations:
        - Neck and arm pain (to allow comparison to ACDF control)
        - Neck pain (Simplify Disc Only)
        - Left arm pain;(Simplify Disc Only)
        - Right arm pain;(Simplify Disc Only

Changes of at least 20 mm on a 100 mm scale will be regarded as clinically significant.

- 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.[1].

- Disc height at each annual timepointcompared to baseline (6 weeks) in the IDE study for the Simplify Disc and for the historical control ACDF, as measured by standard lateral radiograph (spot film, distance of 6 feet, centered at C5 with patient upright).
- Adjacent level deterioration at each annual timepoint compared to baseline in the IDE study for the Simplify Disc and for the historical control ACDF.
- Displacement or migration of the device; only changes of > 3 mm will be considered significant due to the margin of error in radiographic determination of displacement distances.
- Treatment satisfaction at at each annual timepoint for the SimplifyDisc and *for the historical control ACDF.
- Health Survey (SF-12v2) for the Simplify Disc at each annual timepoint compared to baseline in the IDE study.
- Dysphagia Handicap Index (DHI scale) for the Simplify Disc at each annual timepoint compared to baseline in the IDE study.

2.3.7.9 [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

1 Hacker *et al., supra* note 7.

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.3.7.10 [redacted]

[redacted]

2.3.7.11 OTHER OUTCOMES

Range of motion in flexion/extension at the operative level. Cobb angle measurements of the functional spinal unit will be made. Differences in range of motion of at least 2 degrees when compared to baseline in the IDE study will be considered clinically significant. Assessments will include comparison of range of motion at 60 months to baseline in the IDE study for the Simplify Disc and for the historical control ACDF and to normal range of motion at the operative level, based on White and Panjabi[2]. Evaluation of these criteria will be based on anterior/posterior, lateral, and flexion/extension X-rays.

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

2 White and Panjabi: Clinical Biomechanics of the Spine. 2nd ed. Philadelphia, JB Lippincott Co.,1990.

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 significant undesirable clinical occurrence in a subject. Adverse events, whether or not device related, must be reported on the appropriate case report form. Adverse events will be classified based on seriousness, relationship to device and procedure, and severity by the study investigator. 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 Simplify Disc study. Only adverse events which occurred in the Month 36 through Month 60 visits or are continuing from 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

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

Investigators 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.

- Definitely Related: An adverse event that has a strong causal relationship. An adverse event that follows a strong temporal relationship to the use of the device or the procedure, follows a known response pattern, and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies.
- Probably Related: An adverse event that potentially has a causal relationship. The adverse event has a reasonable temporal relationship to the use of the device or the procedure and alternative etiology is less likely compared to the potential relationship to the use of the device or the procedure.
- Possibly Related: An adverse event that potentially has a causal relationship. The adverse event has a reasonable temporal relationship to the use of the device or the procedure but alternative etiology is equally likely compared to the potential relationship to the use of the device or the procedure.
- Not Related: An adverse event without any apparent causal relationship. The adverse event is due to the underlying disease state or is due to concomitant medication or therapy not related to the use of the device or the procedure.

- Unknown Relationship: If the adverse event cannot be determined to have a causal relationship, it will be classified as unknown.

2.3.8.5 Assessment of Severity

- Mild: event/symptom is transient and well tolerated by the patient.
- Moderate: event/symptom causes discomfort and interferes with routine activities of the patient.
- Severe: event/symptom interferes considerably with the routine activities of the patient or causes inability to work.
- 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.

2.3.8.6 Clinical Events Committee

The Clinical Events Committee ("CEC") will adjudicate all adverse events. This will include all UADEs, SAEs, secondary surgeries at the index and adjacent levels, adverse events determined to be "severe", and adverse events deemed definitely, probably and possibly related or with an unknown relationship to the device or procedure. The CEC will review investigator assigned neurological status at 60 months for the Simplify Disc group onlyto determine if neurological status has improved, maintained or declined compared to baseline in the IDE study.

The CEC may determine neurologic status has declined based on changes including:

- Motor Assessment: shift of -1.
- Sensory Examination: shift from normal to abnormal; abnormal to
- increased abnormality.
- Reflex Response: shift from Normal to anything else; hyporeflexive to
- absent; hyporeflexive to hyperreflexive or hyperreflexive to hyporeflexive.
- Clumsiness, Atrophy, Cramping, Spasms and Numbness: shift from
- absent to present.
- Dysphagia (difficulty swallowing) and Dysphonia (difficulty with producing
- sounds resulting in hoarseness, weakness, harshness, roughness and/or
- breathy sound): any worsening.

- Myelopathic Gait Abnormality Class: any worsening
- Assessment: Does the CEC agree with the investigator assessment

The CEC will also adjudicate all protocol deviations. The CEC will consist of three spine surgeons who are not affiliated with the Sponsor or who are not participating in the study. The CEC charter is used for adjudication of both Simplify Disc and historical control ACDF patients. The recommendations of the CEC override the investigator's classification 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 that *does not involve* modification, addition or removal of any components of the device" in the postoperative or follow-up period.
- Revision - any procedure in the postoperative or follow-up period that adjusts modifies or removes part of the original implant configuration *with or without* replacement of a component – may include adjusting the position of the original configuration in the postoperative or follow-up period.
- Removal - a procedure where the entire device is removed with or without replacement of the device in the postoperative or follow-up period.
- Supplemental fixation – a procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement of a rod/ screw system)

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, Inc. 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, Inc Official.

2.5.6 ROLE OF CO-PRINCIPAL INVESTIGATORS

NuVasive, Inc. 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, Inc. 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.