CLINICAL STUDY PROTOCOL

for the

INVESTIGATION

Of The

SIMPLIFY®

CERVICAL ARTIFICIAL DISC

SPONSOR:

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

MARCH 1, 2022

PROTOCOL SIGNATURE PAGE

CLINICAL STUDY PROTOCOL

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SIMPLIFY® CERVICAL ARTIFICIAL DISC

Version March 1, 2022

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

1.1 STUDY SPONSOR

NuVasive, Inc.

7475 Lusk Boulevard

San Diego, CA 92121

Phone: 858-909-1800

[redacted]

1.2 [redacted]

[redacted]

1.3 [redacted]

[redacted]

1.4 [redacted]

[redacted]

2. INVESTIGATIONAL PLAN

2.1 PURPOSE OF STUDY

This study is intended to demonstrate that the Simplify® Disc is at least as safe and effective as conventional anterior cervical discectomy and fusion (ACDF) when used to treat one level between C3 to C7 for cervical degenerative disc disease (DDD) defined as 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 in subjects who are unresponsive to conservative management.

2.2 PROTOCOL STUDY CONDUCT

2.2.1 STUDY DESCRIPTION

This study will utilize a non-concurrent historical control with subject-level data on a parallel group design. The historical control group will be formed from the randomized ACDF arm (N=133) of the recently completed Kineflex®|C Disc trial. Since this control group is essentially from the same population and protocol in which the investigational device is to be studied, adequate control group comparability is expected. Control group comparability will be confirmed using propensity score analysis. This will be done using sub classification through propensity score (PS) quintiles (Rosenbaum and Rubin, 1983)[1]. The PS model will be evaluated according to rigorous criteria (Imbens and Rubin 2015)[2] using a published heuristic (Maislin and Rubin 2010)[3]. PS analysis is capable of identifying cases when there is inadequate comparability to permit valid statistical inference (Yue 2007[4]).

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[1] Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983a, 70:41-55.

[2] Imbens and Rubin D. Causal Inference in the Social and Biomedical Sciences Cambridge University Press 2015 (in press).

[3] Maislin G and Rubin DB. Design of Non-Randomized Medical Device Trials Based on Sub-Classification Using Propensity Score Quintiles, Topic Contributed Session on Medical Devices. Proceedings of the Joint Statistical Meetings 2010, pg 2182-2196.

[4] Yue LQ. Statistical and regulatory issue with the application of propensity score analysis to nonrandomized medical device clinical studies, Journal of Biopharmaceutical Statistics 2007, 17: 1-13.

2.2.2 STUDY OBJECTIVES AND HYPOTHESIS

2.2.2.1 OBJECTIVES

The objective of this clinical study is to evaluate the safety and effectiveness of the Simplify® Disc for treatment of DDD compared to conventional ACDF for reconstruction of the disc space at one level between C3 to C7 for DDD defined as 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 that is unresponsive to conservative management.

2.2.2.2 HYPOTHESIS

The study hypothesis is that in subjects with DDD defined as 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 24 composite clinical success (CCS) rate of the Simplify® Disc will be no worse than conventional ACDF.

- Individual success for the investigational Simplify® Disc is defined as at least a 15 point improvement in NDI Score at 24 months compared with baseline, maintenance or improvement in neurologic status at 24 months compared with baseline, no device failures or revision, reoperation, removal and/or supplemental fixation within 24 months of index procedure; and the absence of major adverse events within 24 months as defined in Section 2.2.6.1 of this protocol.
- Individual success for the control ADCF device is defined as at least a 15 point improvement in NDI Score at 24 months compared with baseline, maintenance or improvement in neurologic status at 24 months compared with baseline, no device failures or revision, reoperation, removal and/or supplemental fixation within 24 months; and the absence of major adverse events within 24 months as defined in Section 2.2.6.1 of this protocol.

2.2.3 STUDY POPULATION

Investigational device patients will be enrolled from up to sixteen (16) sites. Each site will enroll one training case. Clinical results from training cases will be summarized separately from the analysis set used in comparisons to the ACDF control. The study will enroll 150 patients for comparison to control. Participants will be at least 18 years of age, and will have had at least six (6) weeks of prior conservative therapy or the presence of progressive symptoms (e.g., increasing numbness or tingling)

or signs of nerve root compression at one level from C3 to C7 for DDD defined as 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. The definition of DDD will also include the presence of at least one of the following: the presence of spondylosis (defined by the presence of osteophytes or dark disc) on CT or MRI; decreased disc height compared to adjacent levels on radiographic film, CT, or MRI or disc herniation on CT or MRI. Prospective participants must have a Neck Disability Index (NDI score) of at least 40. All subjects who meet the inclusion criteria and do not meet the exclusion criteria, and who elect to participate and sign Informed Consent will be included in the study.

2.2.3.1 INCLUSION CRITERIA

Prospective subjects must meet ***all*** of the inclusion criteria to participate in this clinical study. To be included in the study, the subject must:

- Be between 18 and 60 years of age;
- Have symptoms of cervical degenerative disc disease (DDD) at ***one cervical level*** from C3 to C7 defined as 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 and radiographic evidence of at least one of the following;
    - Spondylosis (defined by the presence of osteophytes or dark disc) on CT or MRI or;
    - Disc height decreased by ≥ 1 mm when compared to adjacent levels on radiographic film, CT, or MRI or
    - Disc herniation on CT or MRI;
- Have at least one of the following radiculopathy or myelopathy symptoms in neck and/or arm;
    - Pain or paresthesias in a specific nerve root distribution from C3 to C7,
    - Decreased muscle strength of at least one level on the 0-5 scale, or
    - Abnormal sensation, including hyperesthesia or hypoesthesia.
- Have at least one of the following:
    - At least six weeks of prior conservative treatment (e.g., physical therapy and/or use of anti-inflammatory medications and muscle relaxants at the manufacturer's recommended therapeutic dose);
    - The presence of progressive symptoms (e.g., increasing numbness or tingling) or
    - Signs of nerve root compression.

- Have a Neck Disability Index (NDI) greater than or equal to 40 on a scale of 100 (moderate disability);
- Be appropriate for treatment using an anterior surgical approach;
- Be likely to return for all follow-up visits[5] and
- Be willing and able to provide Informed Consent for study participation.

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. [6]

For the purpose of this study, conservative therapy may include, but is not limited to, injections of steroids, physical therapy, bracing, traction, acupuncture, yoga, life style changes, neck support or massage chairs, exercise, ice, heat, massage, water therapy, chiropractic, and medications prescribed for pain, muscle tightness, muscle cramping or inflammation of muscles or nerves or other symptoms typically involved with chronic neck conditions such as DDD.

2.2.3.2 EXCLUSION CRITERIA

To qualify for enrollment in this study, patients must meet ***none*** of the exclusion criteria as follows:

- Marked cervical instability on resting lateral or flexion/ extension X-ray (translation > 3 mm or > 11 degrees rotation to that of either adjacent non-treatment level);
- Non discogenic neck pain or non discogenic source of symptoms (e.g., tumor, rotator cuff injury, etc.);
- Radiographic confirmation of severe facet disease or facet degeneration;
- Bridging osteophytes;
- Less than 2 degrees of motion at index level;
- Prior surgery at the level to be treated, except laminotomy without accompanying facetotomy;

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[5] Please note that patients who live significant distances away from a treatment center are statistically likely to be present for treatment, but are not likely to return for all follow-up visits. For this reason, patients who live over **150** miles from a treatment center are not eligible for treatment in this clinical study without **prior approval** from the study Sponsor.
[6] *See* 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).

- Prior fusion or artificial disc replacement at any cervical level;
- More than one neck surgery via anterior approach;
- Previous trauma to the C3-C7 levels resulting in compression or bursting;
- Documented presence of a free nuclear fragment at cervical levels other than the study level;
- Axial neck pain only (no radicular or myelopathy symptoms);
- Symptomatic DDD at more than one cervical level;
- Severe myelopathy (less than 3/5 muscle strength);
- Any paralysis;
- Recent history (within previous six months) of chemical or alcohol dependence;
- Active systemic infection;
- Infection at the site of surgery;
- Prior disc space infection or osteomyelitis in the cervical spine;
- Any terminal, systemic or autoimmune disease;
- Metabolic bone disease (e.g., osteoporosis/osteopenia [7], gout, osteomalacia, Paget's disease);
- Any disease, condition or surgery which might impair healing, such as;
    - Diabetes mellitus requiring daily insulin management,
    - Active malignancy,
    - History of metastatic malignancy.
- Current or extended use (> 6 months) of any drug known to interfere with bone or soft tissue healing;
- Known PEEK, ceramic, titanium allergy;
- Arachnoiditis;
- Significant cervical anatomical deformity at the index level or clinically compromised cervical vertebral bodies at the index level due to current or past trauma (e.g., by radiographic appearance of fracture callus, malunion, or nonunion) or disease (e.g., ankylosing spondylitis, rheumatoid arthritis);
- Currently experiencing an episode of major mental illness (psychosis, major affective disorder, or schizophrenia), or manifesting physical symptoms without a diagnosable medical condition

[7] Patients at risk for osteoporosis/osteopenia must be screened using a dual X-ray absorptiometry scan (DXA). Patients meeting the WHO definition for osteoporosis/osteopenia for risk of fracture,, i.e., have a bone mineral content greater than 1.5 standard deviations below the mean for young, healthy adults (DXA score), are ineligible for study participation.

to account for the symptoms, which may indicate symptoms of psychological rather than physical origin;

- Pregnancy at time of enrollment, or planning to become pregnant, since this would contraindicate surgery [8];
- Use of spinal stimulator at any cervical level prior to surgery;
- Currently a prisoner;
- Currently involved in spinal litigation which may influence the subjects reporting of symptoms **or**
- Participation in any other investigational drug, biologic or medical device study within the last 30 days prior to study surgery.

Subjects will be considered at risk for osteoporosis/osteopenia based on National Osteoporosis Foundation criteria:

- Maternal history of hip fracture [9];
- Chronic renal failure;
- Previous fragility fractures;
- History of having taken doses of corticosteroids in doses > 7.5 mg/day for one year or more;
- Amenorrhea greater than one (1) year in duration {females only – not due to hysterectomy without oophorectomy (simple hysterectomy)}; or
- Menopause (females only – defined as prior diagnosis of menopause or use of hormone replacement therapy for treatment of menopause) prior to age 45;
- Primary hyperparathyroidism or hyperthyroidism.

Additionally, subjects meeting the following criteria will be considered at risk of osteoporosis/osteopenia for the purposes of this study:

- Post thyroidectomy or parathyroidectomy.

Subjects considered at risk of osteoporosis/osteopenia (male and female) based on the criteria above must undergo a *spinal* DXA scan prior to enrollment in the study.

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[8] Pregnancy during participation in this study should also be discouraged, since pregnancy may prohibit exposure to X-rays during necessary follow-up timeframes.
[9] For the purposes of this study, maternal history of hip fracture after the age of 80 will not be considered a risk factor.

Autoimmune disease includes, but is not limited to HIV disease, rheumatoid arthritis, and lupus.

2.2.4 STUDY DESIGN

2.2.4.1 OVERALL STUDY DESIGN

This study will utilize a non-concurrent historical control with subject-level data on a parallel group design. The historical control group will be formed from the randomized ACDF arm (N=133) of the recently completed Kineflex®|C Disc trial. Since this control group is essentially from the same population and protocol in which the investigational device is to be studied, adequate control group comparability is expected. Control group comparability will be confirmed using propensity score analysis. This will be done using sub classification through propensity score (PS) quintiles (Rosenbaum and Rubin, 1983)[10]. The PS model will be evaluated according to rigorous criteria (Imbens and Rubin 2015)[11] using a published heuristic (Maislin and Rubin 2010)[12]. PS analysis is capable of identifying cases when there is inadequate comparability to permit valid statistical inference (Yue 2007[13]).

Each site will be asked to target a minimum of 5 subjects depending on patient availability. No site will be permitted to enroll more than 24 subjects. The first procedure at each site will constitute a training set. Data from the training set will be summarized separately and not used in the primary comparison to control.

Investigators will use an anterior surgical approach. Surgeons will be trained on the technique, selection criteria, and protocol for the Simplify® Disc clinical study prior to their first implantation procedure.

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[10] Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983a, 70:41-55.

[11] Imbens and Rubin D. Causal Inference in the Social and Biomedical Sciences Cambridge University Press 2015 (in press).

[12] Maislin G and Rubin DB. Design of Non-Randomized Medical Device Trials Based on Sub-Classification Using Propensity Score Quintiles, Topic Contributed Session on Medical Devices. Proceedings of the Joint Statistical Meetings 2010, pg 2182-2196.

[13] Yue LQ. Statistical and regulatory issue with the application of propensity score analysis to nonrandomized medical device clinical studies, Journal of Biopharmaceutical Statistics 2007, 17: 1-13.

Subjects will be considered enrolled in the study for the purposes of an intent-to-treat analysis, only after they have been treated (time of incision). Subjects excluded prior to treatment, due to withdrawal of consent, arising medical difficulties (e.g., heart attack), documentation of ineligibility by circumstances unforeseen at the time of Consent, etc. will be considered screening failures. Baseline data, including the reason for exclusion, will be collected for screening failures. However, baseline data for screen failures may not be complete, as the patient may be determined to be a screen failure early in the screening process. All patients enrolled in the study will be included in an "intent to treat" analysis, regardless of failure to complete the required follow-up examinations.

All radiographic endpoints, including in vivo endplate thickness analysis, will be evaluated independently by one core laboratory. Range of Motion will be measured by this core lab using a protocol to determine this measurement incorporating validated computerized techniques to ensure reproducibility.

Neurologic status will be evaluated by a qualified evaluator, who may be an MD, an RN or a PA.

2.2.4.2 CONTROL GROUP

The proposed ACDF control group is from the Sponsor's multi-center, prospective, randomized, non-inferiority clinical trial of the Kineflex|C Disc that was conducted in the United States. This study compared the Kineflex|C Disc to conventional ACDF for treatment of subjects with single level degenerative disc disease (DDD) who are symptomatic at only one level from C3 to C7 that is unresponsive to conservative management. The first subject was treated [redacted] 2005 and the last randomized subject treated was [redacted] 2007. A total of 348 subjects were treated at 21 investigational sites, 192 subjects in the investigational Kineflex|C Disc treatment group (135 randomized and 57 non- randomized), and 134 subjects in the control group (133 randomized and 1 non-randomized) (all randomized in a 1:1 ratio). [redacted] Therefore, the amount of time that has passed is relatively modest when considering that medical practice concerning conventional ACDF is relatively unchanged during this time interval.

The conventional ACDF was performed using [redacted] allograft bone and [redacted] [an anterior cervical plate]. The anterior cervical plate system was fixed into place according to a standard technique. Closure was the same for both the control and the Kineflex|C Disc

device groups and it will be the same for the investigational device. There have been no important changes in the surgical methods pertaining to conventional ACDF.

A particularly strong justification for the use of this historical control is that almost the same set of institutions and surgeons that enrolled patients into the historical control will prospectively enroll patients into the investigational Simplify® Disc group.

In summary, the above factors lead to the reasonable expectation that the design of the observational study using PS sub classes will result in statistical estimates of treatment group differences with acceptably low bias.

2.2.4.3 STUDY DURATION

For the purposes of demonstrating safety and efficacy for marketing approval, each subject will be followed for at least twenty-four (24) months post-treatment. Subjects will continue to be followed thereafter until follow-up is no longer required by FDA. [redacted]

For the purposes of this study, subjects will be evaluated pre-operatively, at treatment, and postoperatively at the postoperative visit (up to 2 weeks post-treatment), and at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 4 weeks), 12 months (± 2 months), 24 months (± 2 months) and annually (± 2 months) thereafter until the last subject enrolled has completed the 24 month evaluation.

2.2.5 STUDY PROCEDURES

2.2.5.1 INFORMED CONSENT

Only patients who sign Informed Consent 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 subjects study file.

2.2.5.2 PRE-TREATMENT EVALUATIONS AND DATA COLLECTION

Pre-treatment evaluations and data collection will include:

- Radiographic studies for verification of DDD;
- AP and lateral X-rays (plain films);
- Flexion-extension X-rays (used to determine range of motion);
- Lateral bending films;
- MRI or CT (investigational group only)
- Radiographic core lab evaluations;
- Dysphagia Handicap Index[14] (investigational group only);
- Study related medical history and physical examination;
- DXA (if indicated as described in Section 2.2.3.2);
- NDI assessment;
- SF-12v2 Health Survey (investigational group only);
- VAS pain assessments (neck and arm; neck, left arm and right arm (investigational group only));
- Neurologic evaluation;
- Study related medication history and
- Work status.

Radiographic studies used for verification of DDD, DEXA scans and baseline MRI or CT may be taken up to 6 months prior to the pre-treatment evaluation. Flexion/extension X-rays and AP & lateral X-rays and lateral bending X-rays must be taken no sooner than 90 days prior to the pre-treatment evaluation. *All other pre-treatment measurements* must be done no sooner than 30 days prior to the pre-treatment evaluation.

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.

For the purposes of this clinical study, only medications taken or administered for the following will be recorded on the Case Report Form:

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[14] Silbergleit, A.K., Schultz, L., Jacobson, B., Beardsley, T. and Johnson, A. The Dysphagia Handicap Index: Development and Validation. Dysphagia 2012, 27:46-52.

- 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.

2.2.5.3 TREATMENT PROCEDURES AND EVALUATIONS

The surgeon will use a standard anterior cervical approach, known as the Smith-Robinson[15] procedure for anterior approach, to the cervical spine. Details of the Smith-Robinson procedure are contained in the Investigator and Study Manuals**.** The diseased disc will be completely removed using a standard technique, decompressing the anterior surface of the spinal canal. If the surgeon believes that the posterior longitudinal ligament is hypertrophic, ossified, or compressing a neurologic structure (e.g., nerve root or spinal cord), the posterior longitudinal ligament will be removed. If the Simplify® Disc cannot be visualized during implantation, a contrast media may be used. The Simplify® Disc will be inserted following the appropriate procedure.

2.2.5.3.1 Simplify® Disc

The surgical technique for implantation of the Simplify® Disc is described in the Simplify® Disc Surgical Technique Guide.

2.2.5.3.2 Historical ACDF Control

[redacted] The anterior cervical plate system was fixed into place according to standard technique, as described above. Closure is the same for both the control and the Simplify® Disc device groups.

2.2.5.3.3 Treatment Evaluations

Treatment evaluations and data collection will include:

- Level treated;

[15] Smith GW, Robinson RA (1958). Treatment of certain cervical spine disorders by anterior removal of the intervertebral disc and interbody fusion. JBJS 40:607-23.

- Implant Position
- Length of surgery (skin-to-skin);
- Condition of posterior ligament
- Amount of blood loss and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

2.2.5.4 POST-TREATMENT EVALUATIONS AND DATA COLLECTION

2.2.5.4.1 Postoperative Care

Following completion of the procedure, subjects will receive treatment according to a standardized postoperative care protocol. According to this protocol, subjects will be permitted to ambulate on the day of surgery, as tolerated. A collar may be worn to support the neck (Philadelphia, Aspen, Miami J, 2 poster orthosis, etc.) until the soft tissues of the neck have healed.

In the Simplify® Disc group, the cervical range of motion will be increased gradually. Subjects will be advised to refrain from heavy lifting (greater than 20 pounds) for 6 weeks and from impact sports for 3 months. Otherwise, they may practice activity as tolerated. Aerobic walking will be stressed for the first 6 postoperative weeks with more resistive exercises using fitness machines after that time.

2.2.5.4.2 Postoperative Evaluations and Data Collection

Data collected postoperatively will include:

- AP and lateral X-rays (plain films);
- VAS pain assessments (neck and arm, neck, left arm and right arm (investigational group only));
- Odom's criteria determination;
- Neurologic evaluation;
- Study-related medications;
- Length of hospital stay and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

2.2.5.4.3 Follow-Up Evaluations and Data Collection

Follow-up evaluations at 6 weeks will include:

- AP and lateral X-rays (plain films);
- Dysphagia Handicap Index (investigational group only);
- NDI assessment;
- VAS pain assessments (neck and arm; neck, left arm and right arm (investigational group only));
- Odom's criteria determination;
- Neurologic evaluation;
- Study-related medications; and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

Follow-up evaluations at 3 and 6 months will include:

- AP and lateral X-rays (plain films);
- Flexion-extension X-rays (used to determine range of motion);
- Lateral bending films (starting at 6 months);
- Radiographic core lab evaluations;
- Dysphagia Handicap Index (investigational group only);
- NDI assessment;
- SF-12v2 Health Survey (6 months for investigational group only);
- VAS pain assessments (neck and arm; neck, left arm and right arm (investigational group only));
- Odom's criteria determination;
- Neurologic evaluation;
- Study-related medications;
- Work status and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

Follow-up evaluations at 12 and 24 months will include:

- AP and lateral X-rays (plain films);

- Flexion-extension X-rays (used to determine range of motion);
- Lateral bending films;
- MRI assessment (investigational group only at 24 month);
- Radiographic core lab evaluations;
- Dysphagia Handicap Index (investigational group only);
- NDI assessment;
- SF-12v2 Health Survey (investigational group only);
- VAS pain assessments (neck and arm; neck, left arm and right arm (investigational group only));
- Odom's Criteria determination;
- Neurologic evaluation;
- Study related medication status;
- Work status;
- Patient satisfaction assessment and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

Subjects who complete their 24 month visit prior to the last study subject's completion of the 24 month visit will continue to be followed annually until the last subject enrolled has completed the 24 month evaluation. However, for the purpose of primary safety and efficacy evaluations, the study completion/ termination assessment will be made at 24 months postoperatively, or at an earlier time point if the subject withdraws or is withdrawn from the study.

Follow-up evaluations annually after 24 months will include:

- AP and lateral X-rays (plain films);
- Flexion-extension X-rays (used to determine range of motion);
- Lateral bending films;
- Radiographic core lab evaluations;
- Dysphagia Handicap Index (investigational group only);
- NDI assessment;
- SF-12v2 Health Survey (investigational group only);

- VAS pain assessments (neck and arm; neck, left arm and right arm (investigational group only));
- Odom's criteria determination;
- Neurologic evaluation;
- Study related medication status;
- Work status;
- Treatment satisfaction assessment and
- Adverse events as defined by Section 2.2.6.1 and Section 2.2.7 of this protocol.
- [redacted]

2.2.5.4.4 Radiographic Assessments

For the purposes of data capture, 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;
- Facet Degeneration;
- Stenosis;
- Modic Changes;
- Cysts and
- Additional Observations.

The in vivo endplate thickness analysis will analyze a consecutive series of the first 25 subjects with required x-rays who complete the 24 month visit and any subject with an explant and/or SAE/severe AE that is judged to be definitely-related to the device. The analysis will be performed using available x-rays from the post-operative, 12 Month, 24 Month visits and annually thereafter as set forth in the core lab protocol.

2.2.5.4.5 [redacted]

[redacted]

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

2.2.5.4.6 Study Completion, Termination or Loss to Follow-up

Subjects are expected to remain in the study for at least 24 months following treatment. Subjects who complete their 24 month visit prior to the last study subject's completion of the 24 month visit will continue to be followed annually until the last subject enrolled has completed the 24 month evaluation. Subjects will continue to be followed thereafter until follow-up is no longer required by

FDA. However, for the purpose of primary safety and efficacy evaluations, the study completion/ termination assessment will be made at 24 months postoperatively, 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 Investigator and Study Manuals. Any subjects with a device removal of the Simplify® Disc will be followed if the subject has not withdrawn consent, in a separate cohort.

2.2.5.5 DATA COLLECTION SUMMARY

Time Point	Pre-op	Tx	Post-op	6 wks	3 mo	6 mo	12 mo	24 mo	Post 24 mo
Informed Consent	X								
DDD assessment (MRI, CT or X-ray)	X								
Medical History & Physical Examination	X								
DXA [a]	X								
AP & Lateral X-rays	X		X	X	X	X	X	X	X
Flexion & Extension X-rays	X				X	X	X	X	X
Lateral bending X-rays	X					X	X	X	X
MRI (or CT at Pre-op only)[c]	X							X	
Radiographic Core Lab Assessments [b]	X		X	X	X	X	X	X	X
Dysphagia Handicap Index	X			X	X	X	X	X	X
NDI	X			X	X	X	X	X	X
SF-12v2 Health Survey	X					X	X	X	X
VAS	X		X	X	X	X	X	X	X
Odom's Criteria			X	X	X	X	X	X	X
Neurologic Exam	X		X	X	X	X	X	X	X
Medications Taken	X		X	X	X	X	X	X	X
Work Status	X				X	X	X	X	X
Treatment Assessments		X							
Treatment Satisfaction Assessment							X	X	X
[redacted]		[redacted]							
Adverse Event Assessment	N/A	As needed							
Study Completion/ Termination	N/A	N/A		As needed					

a. If indicated as described in Section 2.2.3.2 of this Protocol. b. Made by two Core labs using radiographs. c. CT acceptable if MRI not available at Pre-op only.

Study windows:

1. Pre-treatment evaluations;
   a. Radiographic studies used for verification of DDD, DEXA and baseline MRI or CT may be taken up to 6 months prior to the pre-treatment evaluation.
   b. Flexion/extension X-rays, lateral bending and AP & lateral X-rays must be taken within 90 days of pre-treatment evaluation.
   c. *All other pre-treatment measurements* must be done within 30 days of the pre-treatment evaluation.
   d. *Pre-op medications* should include medications taken within 30 days prior to pre-treatment evaluation.
2. Postoperative evaluations must be taken *between 12 hours and 2 weeks* postoperatively, *except postoperative adverse events* which should be captured from the time the subject leaves the operating room up to 4 weeks postoperatively.
3. Follow-up visit evaluations will be taken at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 4 weeks), 12 months (± 2 months), 24 months (± 2 months) and annually thereafter. The study visit window for visits post 24 months is ± 2 months.

2.2.6 STATISTICAL CONSIDERATIONS

2.2.6.1 PRIMARY ENDPOINT

The study hypothesis is that in subjects with DDD defined as 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 24 composite clinical success (CCS) rate of the Simplify® Disc will be no worse than conventional ACDF when success of ACDF is evaluated at Month 24.

- Individual success for the investigational Simplify® Disc is defined as at least a 15 point improvement in NDI Score at 24 months compared with baseline, maintenance or improvement in neurologic status at 24 months compared with baseline, no device failures or revision, reoperation, removal and/or supplemental fixation within 24 months of index procedure; and the absence of major adverse events within 24 months as defined in Section 2.2.6.1 of this protocol.
- Individual success for the control ACDF device is defined as at least a 15 point improvement in NDI Score at 24 months compared with baseline, maintenance or improvement in neurologic status at 24 months compared with baseline, no device failures or revision, reoperation, removal and/or supplemental fixation with 24 months; and the absence of major adverse events within 24 months as defined in Section 2.2.6.1 of this protocol.

Device failure is defined as breakage, migration, or mechanical failure of the components as defined in the Radiographic Evaluation Protocol.

For purpose of determining individual subject success, a major adverse event is defined as any of the following which are definitely related to the device system or to a device component as determined by the CEC:

- Permanent neurologic damage or permanent nerve root injury related to a level at or below the level treated;

- Implant or component breakage or migration that does not require revision, reoperation or removal, but causes persistent or moderate to severe dysphagia[16] and/or
- Subject death.

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

- 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).

2.2.6.2 STUDY SUCCESS

The null hypothesis is that the probability of achieving Month 24 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 24 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 0.05.

2.2.6.3 DESIGN OF THE OBSERVATIONAL STUDY

The 133 control subjects from the Sponsor's prior trial will be used to form a valid control group for determining the safety and effectiveness of the Simplify® Disc device. This will be done using sub classification through propensity score (PS) quintiles (Rosenbaum and Rubin, 1983)[17]. This approach

16 Bazaz R, Lee MJ, Yoo JU, *supra* note 13.

17 Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983a, 70:41-55.

directly addresses potential selection bias inherent in non-randomized comparisons. The PS model will be evaluated according to rigorous criteria (Imbens and Rubin 2015)[18] using a published heuristic (Maislin and Rubin 2010)[19]. Applications of this heuristic have been recently been published (e.g., Keenan, Maislin, et al 2014[20]; Arnardottir, Lim, Keenan, Maislin et al 2014[21]; and Pak, Keenan, Jackson, Grandner, Maislin et al 2014[22]). The heuristic is designed to identify 5 sub classes in which the groups to be compared share the same multivariate distribution of a comprehensive set of baseline variables. Within each sub class, patients are therefore equally likely to have received the Simplify® Disc or conventional ACDF. The propensity score is the observational study analogue of complete randomization in randomized experiments in the sense that its use is not intended to increase precision but only to eliminate systematic biases in treatment-control comparisons (Rubin 2008[23])". Moreover, the "propensity score technique allows the straightforward assessment [of] whether the treatment groups overlap enough regarding baseline covariates to allow for a sensible treatment comparison" (Yue 2007)[24] .

The PS sub classes will be formed when the prospective enrollment is completed. As part of the modeling process it sometimes becomes necessary to iteratively 'shave' off patients from the extremes of the PS distributions in order for the Imbens and Rubin 2015 PS model estimation validity criteria to be met. Where possible, exclusions of control patients will be preferred over investigational device patients in order to maximize generalizability. Results from excluded Simplify® Disc patients will be summarized separately, compared to those in the primary analysis set,

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18 Imbens and Rubin D. Causal Inference in the Social and Biomedical Sciences Cambridge University Press 2015 (in press).

19 Maislin G and Rubin DB. Design of Non-Randomized Medical Device Trials Based on Sub-Classification Using Propensity Score Quintiles, Topic Contributed Session on Medical Devices. Proceedings of the Joint Statistical Meetings 2010, pg 2182-2196.

20 Keenan BT, Maislin G, Sunwoo BY, Arnardottir ES, Jackson N, Olafsson I, Juliusson S, Schwab RJ, Gislason T, Benediktsdottir B, Pack AI. Obstructive sleep apnoea treatment and fasting lipids: a comparative effectiveness study. Eur Respir J. 2014 May 15.

21 Arnardottir ES, Lim DC, Keenan BT, Maislin G, Benediktsdottir B, Juliusson S, Pack AI, Gislason T. Effects of obesity on the association between long-term sleep apnea treatment and changes in interleukin-6 levels: the Icelandic Sleep Apnea Cohort. J Sleep Res. 2014 Oct 31. doi: 10.1111/jsr.12252. [Epub ahead of print].

22 VM Pak, BT Keenan, N Jackson, MA Grandner, G Maislin, K Teff, RJ Schwab, ES Arnardottir, S Júlíusson, B Benediktsdottir, T Gislason, AI Pack. Adhesion molecule increases in sleep apnea: beneficial effect of positive airway pressure and moderation by obesity. Int J Obes (Lond). 2014 Jul 21.

23 Rubin D. For objective causal inference, design trumps analysis. The Annals of Applied Statistics 2008, 2:3:808-840.

24 Yue LQ. Statistical and regulatory issue with the application of propensity score analysis to nonrandomized medical device clinical studies, *Journal of Biopharmaceutical Statistics* 2007, 17: 1-13.

and the potential implications of excluding patients discussed in the PMA. Non-selected control patients are considered to be not enrolled. Only the baseline data used in the PS design will be summarized for excluded controls.

It is important to note that the sequential model building process used to identify an analysis data set for which there is adequate covariate balance within subclasses, poses no concern for Type I error inflation. This is because the PS model building process makes no use of outcome data. To avoid bias, no outcome data will be provided to the statistician (Brendan Keenan) who will be forming the PS sub classes; and the model identification process will be documented in a series of iterations as described in [Maislin and Rubin 2011]. That is, the sequential model-building heuristic should be viewed as part of the 'design of the observational study'. Here 'design' may be interpreted as "contemplating, collecting, organizing, and analyzing of data that takes place prior to seeing any outcome data (Rubin 2008)[25]". At its conclusion, verification of balance between device groups within sub class is easily done through graphical means.

Given the expected similarity of the populations from which the investigational and control groups were obtained and the specificity of the clinical indication, it is expected that no more than 20% of the ACDF historical controls and 10% of the investigational device group will need to be excluded in order to identify sub classes that meet the Rubin criteria for validity.

We acknowledge that because the proposed propensity score design can only assess the comparability of the two groups after the current study has been completed, there can be significant risk that in the end the data may not be comparable. The sample size determination assumes that at most 20% of the ACDF historical and at most 10% of the investigational device patients will be excluded in the iterative heuristic used to construct PS sub classes that meet Rubin's validity criteria. The risk of insufficient sample sizes due to such exclusion can be reduced, by continuing enrollment into the investigational device group. For example, suppose a valid PS design is identified that excludes many more controls than expected but excluded only a very tiny fraction of investigational device patients. Then, the reduction in power due to a smaller control group sample size can be recovered by

25 Rubin D. For objective causal inference, design trumps analysis. The Annals of Applied Statistics 2008, 2:3:808-840.

continuing enrollment into investigational arm until the original power target is maintained and then performing a new sub classification.

All components necessary to formulate the relevant composite clinical endpoints are available in both studies. Any differences in endpoint evaluation are due to the nature of the difference between artificial discs and fusion procedures. The components of the CCS were evaluated in the same fashion for the ACDF control as they are to be evaluated prospectively for Simplify® Disc enhancing comparability of results from the two studies. This includes use of the same independent radiography core, [redacted]. Although composite clinical success requires a threshold improvement in the Neck Disability Index (NDI), the "NDI is the oldest and most widely used instrument for self-reporting of disability due to neck pain. Its internal psychometric properties have been well established in numerous cultural groups with neck pain: it is highly reliable, strongly internally consistent, and with a 1-factor structure for "physical disability." It has strong and well-documented convergent and divergent validity with other instruments used in the evaluation of patients and subjects with neck pain" (Vernon 2008)[26]. The minimum clinically important difference in cervical spine fusion surgery was established to be 15 points out of 100 (Carreon, Glassman and Campbell 2010)[27] .

In summary, the above factors lead to the reasonable expectation that the design of the observational study using PS sub classes will result in statistical estimates of treatment group differences with acceptably low bias.

2.2.6.4 Sample Size Analysis

For the control group, prior analysis utilized an endpoint that was summarized as follows: "Overall success requires success on each component including: 15 point improvement in NDI score, no device failure, no supplemental index surgery failure, no major adverse event, and no neurological deterioration (assessed through 24 months only)." These results were used to

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26 Vernon H. The Neck Disability Index: State of the Art 1991-2008. Journal of Manipulative and Physiological Therapeutics 2008, September 491-502.
27 Carreon LY, Glassman SD, Campbell MJ et al. Neck Disability Index, short form-36 physical component summary, and pain scales for neck and arm pain: the minimum clinically important difference and substantial clinical benefit after cervical spine fusion. *Spine J.* 2010;10:469-74.

inform the sample size justification since the endpoint is similar to the endpoint to be used in the proposed study. At Month 24, 116 of 133 (87.2%) ACDF controls were evaluable for Month 24 CCS and 78 of these 116 (67.2%) achieved Month 24 CCS. For the Kineflex|C investigational arm, 118 of 136 (86.7%) patients were evaluable for overall success and overall success was achieved in 95 of 118 (80.5%) patients and 82 of 116 (70.7%), respectively. For the purpose of sample size determination, it was assumed that patients implanted with the Simplify® Disc would have an expected Month 24 overall success rate equal to 80.5%, the value observed for the Kineflex|C group at Month 24.

As noted above, the fusion component of the composite clinical success endpoint is removed from the primary endpoint. A re-analysis of the final data set was performed with the aim of determining the numbers and percentages of patients achieving the composite endpoint with the fusion component removed from both device groups. It was observed that for Kineflex|C, the success rate increased only slightly from 80.5% (95/118) to 81.4(%). In contrast, for the fusion control group to be used in the current study, the success rate increased from 67.2% (78/116) to 74.1 (%). The estimated device group difference was reduced from 13.3% to 7.3%.

It is assumed for the purpose of sample size analysis that at least 80% of the 116 evaluable ACDF controls, that is, N=93 will be remaining after the iterative PS sub classes determination and that the success rate will be 74.1% in the retained sample. It is possible that the effective sample size will be slightly higher since, as described below, multiple imputation will be used to address missing data from the prior study.

In order to have a sufficient size sample for safety profile evaluation, 150 investigational device patients will be enrolled. For the purpose of sample size evaluation, this value is reduced by 15% to account for loss-to-follow-up. It is further assumed that no more than 10% of the analysis set will be excluded based on design of the PS sub classes, reducing the evaluable sample size from 128 to 115.

The assumptions above imply an expected device group difference equal to equal to 7.3% for the primary endpoint. The study is designed to demonstrate non-inferiority using a non-inferiority margin equal to -10.0%.

If there were N=115 Simplify® Disc patients, then a "two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level will have 91% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, $\pi_1 - \pi_2$, is -

0.10 or farther from zero in the same direction) in favor of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0.073 and the proportion in the standard group is 0.741 [redacted]).

Thus, as long as the superiority margin between the Simplify® Disc and ADCF about the same as observed between Kineflex|C and ADCF, then N=115 patients included in the Simplify® Disc analysis set will result in adequate (i.e., ≥80%) statistical power. As noted above, this sample size is conservatively increased by 15% to account for potential loss-to-follow-up and by 10% to account from exclusions during the PS modeling. Therefore, the target prospective enrollment is N=150.

2.2.6.5 PROPENSITY SCORE MODELING APPROACH

A sequential heuristic for PS modeling will be used to determine the PS model (Maislin and Rubin 2011). The heuristic is capable of producing balance between groups that are prerequisite for valid efficacy comparisons. The heuristic includes a trio of "stages" that may be repeated as many times as necessary. These stages include (1) estimating a main effects PS model; (2) identification of required higher order terms through evaluation of within subclass bias effect sizes and other relevant PS diagnostic information; and (3) exclusion of subjects in one treatment group with insufficient 'covariate overlap'. The magnitudes of standardized effect sizes for group differences in linear, squares, and cross-product terms within subclasses provide key insight into what additional terms the PS model must have in order to achieve adequate within-subclass balance between treatment groups. Specific choices made during the model building process pose no concern for Type I error inflation because these analyses do not involve any outcome data. In this way the sequential model-building exercise should be viewed as part of the 'design of the observational study'. The result of the PS modeling process is an assignment of patients from both groups to sub classes defined on the basis of the estimated propensity scores. When certain diagnostic properties hold, the covariate distributions are identical between the investigational and control groups within each of the PS quintiles. Therefore, within PS quintile, patients are essentially equally likely to be in either group based on relevant covariates and analyses can proceed as if patients were randomized. This is accounted for by including a df=4 factor for propensity score quintile in analysis of variance and regression models. The ability of the propensity score model to balance observed covariates will be graphically assessed.

2.2.6.6 SUPERIORITY TESTING

If the non-inferiority study success criterion is met, superiority testing will be performed in the intent-to-treat 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.

2.2.6.7 ADDRESSING MISSING 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.

2.2.6.8 PLANS TO ASSESS SITE POOLABILITY

Assessment of site poolability for the likelihood of achieving primary CCS will be performed for sites enrolling patients into the Simplify® Disc group. This assessment will involve estimating the parameters of a random effects meta-analysis. The observed site-specific success rates will be subjected to an arcsine in order to remove the dependence of within site variance and expected success rate (Freeman and Tukey, 1950)[28]. This permits application of the DerSimonian and Laird random effects meta-analysis approach. The R function ***metaprop*** in the R package ***meta*** deals

28 Freeman MF & Tukey JW. Transformations related to the angular and the square root. Annals of Mathematical Statistics 1950, 21, 607–611.

implements DerSimonian and Laird[29] random effects meta-analysis using an arcsine transformations and so this software will be used. This package requires the numbers of events and total sample size for each study to be provided as arrays.

The transformed success probabilities are assumed to follow a normal distribution with mean μ and variance τ^2. The magnitude of site-to-site variability in primary CCS for the Simplify® Disc will be quantified using the I^2 statistics (Higgins et al 2004[30]). I^2 is the fraction of $\boldsymbol{\tau^2}$ that is due to effect size heterogeneity, as opposed to sampling variance. Higgins *et al* indicate that, "A naive categorization of values for I^2 would not be appropriate for all circumstances, although we would tentatively assign adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%".

Therefore, the key quantitative assessment of whether or not site-to-site variability is important will involve the comparison of the observed I^2 value for the prospective study to the above guidelines. In addition to I^2, the statistical significance of the site-to-site variability will be determined using the Q statistic with degrees-of-freedom equal to the number of sites minus 1. Sites contributing less than 6 patients will be combined prior these analyses.

2.2.6.9 [redacted]

[redacted]

[redacted]

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

29 DerSimonian R and Laird NM. Meta-analysis in clinical trials. Journal of Controlled Clinical Trials, 1986; 7:177-188.

30 Higgins JP, Thompson SG, Deeks JJ, and Altman DG. Measuring inconsistency in meta-analysis. BMJ 2003, 327(7417): 557-560.

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2.2.6.10 [redacted]

[redacted]

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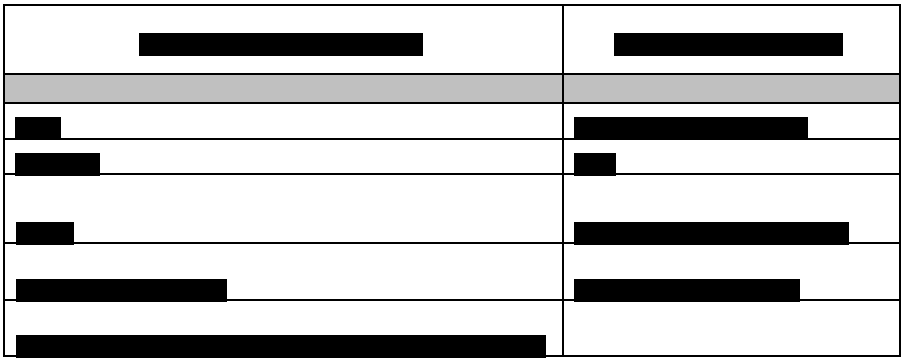

2.2.6.11 SECONDARY ENDPOINTS

Secondary endpoints include:

- Clinically significant improvement in one or more radicular symptoms or myelopathy at 24 months compared to baseline for the investigational Simplify® Disc and 24 months compared to baseline for the 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
        - Left arm pain;
        - Right arm pain;

        .

        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.[31].

- Time to recovery (time to first 15-point NDI improvement).
- Disc height at 24 months compared to baseline for the investigational Simplify® Disc and at 24 months compared to baseline for the control ACDF, as measured by standard lateral radiograph (spot film, distance of 6 feet, centered at C5 with patient upright).
- Adjacent level deterioration at 24 months compared to baseline for the investigational Simplify® Disc and at 24 months compared to baseline for the 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 24 months for the investigational Simplify® Disc and at 24 months for the control ACDF.
- Health Survey (SF-12v2) for the investigational Simplify® Disc at 24 months compared to baseline.
- Dysphagia Handicap Index (DHI scale) for the investigational Simplify® Disc at 24 months compared to baseline.
- Facet deterioration for the investigational Simplify® Disc at 24 months compared to baseline..
- Results at 24 months for the investigational Simplify® Disc and at 24 months for the control ACDF will also be categorized by the physician according to Odom's Criteria, as described below.

Excellent	Improvement in most (at least 80%) of the preoperative signs and symptoms, with little deterioration (not more than 10%)
Good	Improvement in some (at least 70%) of the preoperative signs and symptoms, with some deterioration (not more than 15%)
Fair	Improvement in half (at least 50%) of the preoperative signs and symptoms, with some deterioration (not more than 20%)
Poor	Improvement in few (less than 50%) of the preoperative signs and symptoms, or significant deterioration (more than 20%)

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

2.2.6.12 OTHER OUTCOMES

Other outcomes to be measured include:

- Duration of hospitalization;
- Blood loss;
- Operative time;
- 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 will be considered clinically significant. Assessments will include comparison of range of motion at 24 months to baseline for the Simplify® Disc and at 24 months compared to baseline for the control ACDF and to normal range of motion at the operative level, based on White and Panjabi[32]. Evaluation of these criteria will be based on anterior/posterior, lateral, and flexion/extension X-rays.
- In vivo endplate thickness analysis on 25 subjects.

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.

2.2.7 SAFETY ASSESSMENT

2.2.7.1 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

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

device will be documented in the patient's pre-operative medical history. Only adverse events which are new or have worsened during the course of this study will be evaluated in the safety assessment.

2.2.7.2 SERIOUS ADVERSE EVENTS (SAE)

2.2.7.2.1 Description

A Serious Adverse Event 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.

2.2.7.3 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

2.2.7.3.1 Description

An Unanticipated Adverse Device Effect 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.

2.2.7.3.2 Reporting

Serious Adverse Events and Unanticipated Adverse Device Effects 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 effect. SAEs and UADEs must also be reported to the approving IRB per the IRB's reporting requirements.

2.2.7.4 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.

2.2.7.5 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.

2.2.7.6 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 24 months to determine whether it meets the criteria for primary endpoint failure as defined as new or worsened decline in neurological status compared to baseline which persists to 24 months based on assessments of motor, sensory, reflex, clumsiness, atrophy, cramping, spasms, numbness, dysphagia, dysphoia, and myelpathic gait abnormality.

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 GaitAbnormality Class: any worsening
- Assessment: Does the CEC agree with the investigator assessment

Adverse events determined to be definitely related to the device system or device component will be further evaluated for potential classification as a 'Major Adverse Event' as defined in section 2.2.6.1 of this protocol.. 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 protocol is designed to mirror the CEC protocol used for the control fusion patients. The recommendations of the CEC override the investigator's classification and become part of the clinical trial data set.

2.3 RISK ANALYSIS

2.3.1 RISKS

Information on the adverse events or complications relating to general and cervical surgery or the investigational spinal system will be collected during the course of the study. Adverse events that may be associated with the investigational spinal system, fusion control, and/or the surgical procedure required for implantation of each device include the following:

Potential risks associated with general surgery include:

- Adverse reaction or allergy to the anesthesia medications
- Heart and vascular complications
  - Cardiac Event
  - Excessive bleeding or injury to blood vessels
  - Edema
  - Hematoma or seroma
  - Hypotension
  - Hypertension
  - Ischemia
  - Embolism including pulmonary embolism
  - Thrombosis
  - Thromboembolism
  - Thrombophlebitis
  - Stroke
- Wound complications
  - Infection of the surgical wound or surrounding soft tissues (e.g., abscess, cellulitis)
  - Wound necrosis
  - Scarring of tissue around the surgical wound
  - Wound dehiscence
  - Wound pain
- Gastrointestinal or urogenital complications
  - Ileus
  - Nausea or vomiting
  - Difficulty with urination
  - Urinary tract infection

- Other
  - Pneumonia
  - Atelectasis
  - Systemic infection
  - Seizures or convulsions

- Inability to resume activities of normal daily living
- Injury to nerves, muscles, or organs
- Pregnancy complications, including miscarriage or fetal birth defects
- Pain
- Psychological Illness
- Death

Potential risks associated with anterior cervical (neck) spine surgery include:

- Risks to neurological structures
  - Dural injury
  - Arachnoiditis
  - Compressive neuropathy
  - Neurologic deterioration -injury to nerves or nerve roots associated with the spinal cord resulting in:
    - pain,
    - weakness,
    - paralysis,
    - altered reflexes,
    - numbness,
    - tingling, or
    - other changes in sensation
  - Coordination abnormalities
  - Dysphasia
  - Gait disturbance
  - Headache
  - Otitis media
  - Tremors
  - Cerebrospinal fluid leakage
  - Cerebrospinal fistula
  - Reflex Sympathetic Dystrophy (RSD)
- Risks to spine structures
  - Annular ossification
  - Development of disc degeneration at adjacent levels
  - Facet joint degeneration
  - Infection of the disc, bone, or surrounding soft tissue

  - Inflammatory conditions, such as discitis
  - Loss of disc height
  - Undesirable change in lordosis
  - Scarring
  - Soft tissue damage
  - Spinal instability
  - Spondylosis
  - Spondylolisthesis
  - Spinal stenosis
- Risks to structures of the neck
  - Airway obstruction
  - Dysphagia,
  - Sore throat
  - Aspiration
  - Dysphonia
  - Hoarseness
  - Laryngeal palsy
  - Vocal cord paralysis
  - Esophageal perforation
  - Pharyngeal perforation
  - Tracheal perforation
  - Vessel damage and/or rupture
  - External chylorrhea
  - Fistula
  - Lymphadenopathy

Potential risks associated with cervical total disc replacement surgery (including with the Simplify® Disc):

- Device Position and Condition
  - Breakage,
  - Disassembly,
  - Loosening,
  - Malposition,
  - Subsidence
  - Migration

  - Improper sizing of the device
- Anatomical difficulties during the surgery
- Adverse reaction or allergy to the device materials (PEEK, ceramic, titanium)
  - Autoimmune disease
  - Metallosis
  - Adverse tissue reaction
  - Osteolysis or vertebral inflammation related to wear debris
  - Tumor formation
- Interference with radiographic imaging because of the presence of the device
- Adverse reaction or allergy to contrast media
- Difficulties with Surgical Instrument
  - Improper positioning or placement of surgical instruments
  - Instrument damage or breakage
  - Improperly cleaned instruments
  - Possibility that an instrument fragment may be left in the body
- Device/joint noise
- The need for 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)
- The need for additional surgery at the level above or below the treated spinal level
- Vertebral fracture

- The development of a new or recurrent spinal problem at the surgery level, or the development of a new spinal problem at the level above or below the treated spinal level
  - Pain
  - Neurological deterioration
  - Heterotopic ossification
  - Spontaneous fusion

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

2.3.2 MINIMIZATION OF RISKS

Adequate measures have been taken to minimize all of the above risks prior to initiation of a U.S. pivotal clinical study, including proper design specification and review, preclinical testing, and clinical evaluations outside the United States. The study Sponsor will provide appropriate training to each investigator prior to each site's respective study initiation. Surgeons will be trained on the technique, selection criteria, and protocol for the clinical study prior to their first implantation procedure. The training will address topics such as the indications and contraindications for the use of the device, the surgical procedure, and selection of appropriate implant sizes, device instrumentation, management of adverse events, and postoperative care and follow-up.

The Sponsor will provide training to the operating room staff at each investigational site. This training will be presented by experienced surgeons, operating room staff, and/or qualified representatives of NuVasive, and will address topics such as the labeling and handling of the Simplify® Disc, the implantation instruments, and the selection of appropriate implant sizes.

Investigators will assess the possible presence of the risks associated with the surgery and with each device during the study treatment and at each follow-up visit by physical and/or radiologic examination and subject interview as applicable.

2.3.3 RATIONALE FOR THE INVESTIGATION

Although many of these risks are significant, they are infrequent. If an unforeseen event arises the subject may be fused in a standard accepted manner (with or without removing the device). Also, it is believed that the use of an artificial total disc may result in return to normal activities of daily living sooner than with fusion, since it is not necessary to wait (at least 6 months) for the vertebrae to fuse

postoperatively. In addition, the MRI imaging of the Simplify® Disc may also be of benefit because it is MR-compatible.

Moreover, if implantation with the Simplify® Disc produces a successful result, it may reduce the subject's symptoms of pain and dysfunction. While pain may also be relieved by fusion, total disc replacement with the Simplify® Disc permits normal or relatively normal segmental motion at the treatment level, and potentially prevents or minimizes the negative impact that fusion has on adjacent vertebral levels. Thus, the potential benefit of the use of the Simplify® Disc merits clinical study.

2.4 DEVICE DESCRIPTION

The Simplify® Disc is designed to be used as a replacement for a degenerated or diseased cervical disc at one level from C3 to C7 that is unresponsive to conservative management in subjects with single-level degenerative disc disease (DDD) with related pain. The spinal system is a 3-piece design consisting of 2 polyetheretherketone (PEEK) end-plates with a plasma-sprayed titanium endplate coating and a fully articulating ceramic alumina matrix composite (AMC) core. The system is available in 3 foot print sizes (Size 1 – 12mm x 15mm, Size 2 - 14 mm x 16 mm and Size 3 - 16 mm x 18 mm) and 3 heights (4mm, 5mm and 6mm). Furthermore, there are 6 additional lordotic configurations (5 deg., Size 1 (height 4mm and 5mm), and Size 2 and Size 3 (height 5mm and 6mm) and 2 coatings (original and enhanced visibility or EV). Each superior/inferior endplate pair is specifically designed for each configuration (i.e. 2 footprint and height). In addition to serrated surfaces, the inferior endplate has inline keels and the superior endplate has two to three teeth to facilitate endplate fixation. Each superior endplate features a retention ring intended to mat with the retention feature of the Simplify core. For standard Simplify® Disc configurations, the Simplify core is 5mm tall, is bi-convex with a radius of R 9.6 mm. The core for the Simplify® Disc with lower height configurations is 4mm tall and bi-convex with a radius of R 7.7mm. The system is packed preassembled and placed as one unit, by means of the insertion instrument.

2.5 STUDY MONITORING

2.5.1 MONITORING ORGANIZATION

Study monitoring functions, with assistance from the Sponsor or designee for pre-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 visits and review of study documents and results. The monitoring organization will be provided with appropriate training regarding the device under investigation and will operate under written procedures to ensure compliance with the protocol.

2.5.2 MONITORING VISITS

On-site 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, is intended to provide an opportunity to review the Investigational Plan with the Investigator and to ensure that the Investigator:

- Has appropriate training, facilities, subject load, time and willingness to comply with study requirements;
- Has the approval of the supervising Institutional Review Board (IRB);
- Has all study documentation and required records on site and
- Assumes responsibility for the investigation at her/his center.

Periodic visits are intended to assess adherence to the Investigational Plan, maintenance of Records and Reports, accountability of investigational devices; 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 that have been treated under the study. If a periodic visit cannot be performed on-site because of compelling circumstances, such as COVID-19, a remote visit may be performed.

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 and review study closure reponsibilites.

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 is recorded for all study subjects for whom Informed Consent is obtained; and that no study treatments are administered 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, Serious Adverse Events, and Unanticipated Adverse Device Effects. Data problems will be addressed in calls to the investigational 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 INITIAL DEVICE IMPLANTATIONS

A Sponsor representative will attend initial device implantations to provide assistance with study management issues, such as device record keeping. A data review with the Investigator by the study monitor will be held prior to or after a few initial implantations to assure adherence to the study protocol and to provide guidance to avoid continuing problems with study procedures and data collection.

2.5.5 REVIEW OF STUDY DOCUMENTS

The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. 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, including pre-study visits, on-site visits or final visit reports, submitted by a site monitor will be reviewed by the senior monitor. The monitor will assume responsibility for any corrective action.

2.5.6 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:

- Review the protocol, CRFs, IDE, and at study completion, the PMA;
- 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.

2.5.7 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, CRFs, IDE, and at study completion, the PMA;
- 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.

2.5.8 DISPOSITION OF STUDY DEVICES AND DATA

All investigational devices received and used by the investigator will be inventoried and accounted for throughout the study. The Simplify® Disc if stored at the investigational site will be stored in a

secure area with restricted access, separate from other medical devices. When instructed by the study Sponsor, the investigator will return any remaining devices, accompanied by a Device Return Form supplied by the study Sponsor. The investigator will not supply investigational devices to any person except those designated by him/her as co-investigators. 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 LABELING

The surgical manual, all implants and instruments will be labeled according to federal regulations (21CFR 812.5) and FDA's Guidance Document for the Preparation of IDEs for Spinal Systems, including the following statement:

> CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use.

2.7 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. Since this is elective surgery, this discussion may be held weeks or months prior to any study surgery. The subject may elect to enter the study at this time, or at sometime later. The investigator or the study coordinator, as appropriate, may answer additional questions the subject may have at an additional office visit or by telephone. Due to the extended time of the consent process, 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 sites 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 subjects study file.