CLINICAL STUDY PROTOCOL

FOR THE

INVESTIGATION

Of The TWO LEVEL

SIMPLIFY® CERVICAL ARTIFICIAL DISC

SPONSOR:

NuVasive, Inc.

7475 Lusk, Blvd.

San Diego, CA 92121

Phone: 858-909-1800

JULY 15, 2021

PROTOCOL SIGNATURE PAGE

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SIMPLIFY® CERVICAL ARTIFICIAL DISC

Version July 15, 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

1.1. STUDY SPONSOR

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

[redacted]

1.2. [redacted]

[redacted]

1.3. [redacted]

[redacted]

[redacted]

1.4. [redacted]

[redacted]

1.5. [redacted]

[redacted]

1.6. [redacted]

[redacted]

2. BACKGROUND

2.1. DESCRIPTION OF CONDITION

Cervical radiculopathy, compression of one or more nerve roots in the cervical spine, or myelopathy, spinal cord compression, are conditions that can result from degenerated and/or diseased discs in the cervical spine. The true prevalence of cervical radiculopathy is uncertain; however, it is estimated that 51% of adults experience neck and arm pain at some time in their life.[1] A primary cause of these symptoms is degeneration of cervical intervertebral discs due to aging. The resultant pain and neurologic symptoms may lead to significant disability. These conditions are not always isolated to one vertebral level.[2] Rather, these conditions are documented to manifest in more than one cervical level for a number of reasons.[3]

2.2. CURRENT THERAPIES

There are several other alternatives for the treatment of intractable radiculopathy or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces at two contiguous levels.

- Traditional options for managing radiculopathy or myelopathy range from conservative modalities, such as rest, wearing a neck brace, heat electrotherapy, physical therapy, and analgesics.
- Surgical alternatives include, but are not limited to, surgical decompression and/or fusion using various bone grafting techniques or interbody fusion devices, which may or may not be used in conjunction with anterior cervical plating (e.g., plate and

1 Furman MB, Cervical Disc Disease. Available at http://www.emedicine.medscape.com/article/305720-overview#A6

2 Bryan VE Jr Cervical motion segment replacement Eur Spine J (2002) 11(Suppl.s):S92-S07

3 Fay LY, Huang WC, Tsai TY, Wu JC, Ko CC, Tu TH, Wu CL, Cheng H. Differences between arthroplasty and anterior cervical fusion in two-level cervical degenerative disc disease. Eur Spine J. 2014 Mar;23(3):627-34.

screws, or posterior spinal systems (e.g., rods, hooks, wires). Anterior cervical discectomy and fusion (ACDF) with an interbody graft or spacer is the most commonly used method for decompression.

The significant limitations of traditional options and spinal fusion procedures have resulted in on-going efforts to develop motion preserving cervical disc prosthesis for both single level and for multi-level use. There are several commercially available artificial disc prostheses for single-level use in the cervical spine. LDR Spine's Mobi-C© received FDA approval on August 23, 2013, thus becoming the first artificial disc to be commercially available in the U.S. for two-level use in the cervical spine. Recently, Medtronic also received FDA approval for Prestige LP™ to be used at two contiguous levels (July 7, 2016).

Each alternative has advantages and disadvantages.[4] [5]

4 Sasso RC, Smucher JD, Hacker, RJ, Heller JG, (2007) Artificial disc versus fusion. Spine 32(26):2933-2940

5 Veeravagu A, Cole T, Jiang B, Ratliff JK, (2014) The Spine Jour 1125-1131

3. INVESTIGATIONAL PLAN

3.1. PURPOSE OF STUDY

This study is intended to demonstrate that the Simplify® Cervical Artificial Disc (Simplify Disc) is at least as safe and effective as conventional anterior cervical discectomy and fusion (ACDF) when used to treat two contiguous discs from C3 to C7 following discectomy at two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces in subjects who are unresponsive to conservative management.

3.2. PROTOCOL STUDY CONDUCT

3.2.1. STUDY DESCRIPTION

This study will be a multi-center, non-randomized study of the two-level Simplify Disc conducted in the United States. There will be up to 18 sites in the United States enrolling a total of N=182 subjects (exclusive of the training subjects). This study will utilize a non-concurrent control with subject-level data in a parallel group design. The historical control group will be formed from the randomized ACDF arm (N=188) of [redacted]. Control group subjects are from a similar population in which the investigational device is to be studied; therefore, adequate control group comparability is expected. The primary effectiveness comparison between the investigational device and the control device will be 'designed' using sub classification through propensity score (PS) quintiles (Rosenbaum and Rubin, 1983)[6] in order to minimize potential selection bias in the estimated device group difference in Month 24 composite clinical success rates. The PS model will be evaluated

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

according to rigorous criteria (Rubin 2001[7]; Imbens and Rubin 2015)[8] using a published heuristic (Maislin and Rubin 2010)[9]. PS analysis is capable of identifying cases when there is inadequate comparability to permit valid statistical inference (Yue 2007[10]).

3.2.2. STUDY OBJECTIVES AND HYPOTHESIS

3.2.2.1. OBJECTIVES

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

3.2.2.2. HYPOTHESIS

The study hypothesis is that in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces at two contiguous levels from C3 to C7 that are unresponsive to conservative management, the Month 24 composite clinical success (CCS) rate of the two-level Simplify Disc is not clinically inferior to conventional two-level ACDF when success is evaluated at Month 24. A non-inferiority margin of $\delta = -0.10$ has been specified.

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

8 Imbens GW and Rubin DB. Causal Inference in the Social and Biomedical Sciences Cambridge University Press 2015.

9 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.

10 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.

Overall success is a composite endpoint which will require the following for success:

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

Overall success will be determined based on data collected during the initial 24 months of follow-up.

3.2.3. STUDY POPULATION

The investigational device population will include 182 subjects enrolled from up to 18 sites in the United States. Subjects will receive the two-level investigational device (Simplify Disc). Each site will also enroll one patient for the purpose of investigational device training. Clinical results from training cases will be summarized separately from the analysis set used in comparisons to the ACDF control. The candidate ACDF control population includes 188 subjects enrolled from [redacted] sites. All enrolled subjects from both device groups 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 signs or symptoms (e.g., increasing numbness, tingling or decreased reflexes) at two contiguous levels from C3 to C7 for intractable radiculopathy (arm pain and /or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces. This will include the presence of spondylosis (defined by the presence of osteophytes) on computed tomography (CT) or magnetic resonance imaging (MRI) and/or herniated nucleus pulposus on CT or MRI. Prospective participants must have a Neck Disability Index (NDI score) of at least 30. 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.

3.2.3.1. INDICATIONS FOR USE

Simplify Disc is indicated for use in skeletally mature patients for reconstruction of two contiguous discs from C3-C7 following discectomy at two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain, or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces and at least one of the following conditions confirmed by imaging (e.g., computed tomography (CT), magnetic resonance imaging (MRI), X-rays): herniated nucleus pulposus and/or spondylosis (defined by the presence of osteophytes). Patients should have failed at least six weeks of non-operative treatment or have had the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management prior to implantation of the Simplify Disc. The Simplify Disc is implanted using an anterior approach.

3.2.3.2. 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:

- Has cervical degenerative disc disease at two (2) adjacent cervical levels (from C3-C7) requiring surgical treatment and involving intractable radiculopathy, myelopathy, or both;
- Has a herniated disc and/or osteophyte formation at each level to be treated that is producing symptomatic nerve root and/or spinal cord compression. The condition is documented by patient history (e.g., neck pain with arm pain, functional deficit and/or neurological deficit), and the requirement for surgical treatment is evidenced by radiographic studies (e.g., CT, MRI, x-rays, etc.);
- Has been unresponsive to non-operative treatment for at least six weeks or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management;
- Has no previous surgical intervention at the involved levels or any subsequent planned/staged surgical procedure at the involved or adjacent level(s);

- Must be at least 18 years of age and be skeletally mature at the time of surgery;
- Has a preoperative Neck Disability Index (NDI) ≥ 30;
- Has a preoperative neck pain score ≥ 8 based on the preoperative Neck and Arm Pain Questionnaire;
- If a female of childbearing potential, patient is non-pregnant, non-nursing, and agrees not to become pregnant during the study period;
- Is willing to comply with the study plan and sign the Patient Informed Consent Form.

Muscle strength will be graded for the deltoid (C5), biceps (C6), and triceps (C7) according to a 6-point scale where 0 = total paralysis, 1 = palpable or visible contraction; 2 = active movement without gravity; 3 = active movement against gravity; 4 = active movement against some resistance; and 9 = normal response (active movement against full resistance).[11]

3.2.3.3. EXCLUSION CRITERIA

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

- Has a cervical spinal condition other than symptomatic cervical DDD requiring surgical treatment at the involved levels;
- Has documented or diagnosed cervical instability relative to adjacent segments at either level, defined by dynamic (flexion/extension) radiographs showing:
    - Sagittal plane translation > 3.5 mm, or
    - Sagittal plane angulation > 20°;
- Has more than two cervical levels requiring surgical treatment;
- Has a fused level (or artificial disc replacement) adjacent to the levels to be treated;

[11] *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).

- Has severe pathology of the facet joints of the involved vertebral bodies;
- Has had previous surgical intervention at either one or both of the involved levels or at adjacent levels;
- Axial neck pain only (no radicular or myelopathy symptoms);
- Has been previously diagnosed with osteopenia or osteomalacia;
- Has any of the following that may be associated with a diagnosis of osteoporosis (if "Yes" to any of the below risk factors, a DEXA Scan will be required to determine eligibility):
    - Postmenopausal non-black female over 60 years of age who weighs less than 140 pounds;
    - Postmenopausal female who has sustained a non-traumatic hip, spine, or wrist fracture;
    - Male over the age of 70;
    - Male over the age of 60 who has sustained a non-traumatic hip or spine fracture.
    - If the level of bone mineral density is a T score of -1.5 or lower (i.e., -1.6, -1.7, etc.), then the patient is excluded from the study
- Has presence of spinal metastases;
- Has overt or active bacterial infection, either local or systemic;
- Has insulin-dependent diabetes;
- Has chronic or acute renal failure or prior history of renal disease;
- Known PEEK, ceramic, titanium allergy;
- Is mentally incompetent (if questionable, obtain psychiatric consult);
- Is a prisoner;
- Is pregnant[12];

[12] Pregnancy during participation in this study should also be discouraged, since pregnancy may prohibit exposure to X-rays during necessary follow-up timeframes.

- Is currently an alcohol and/or drug abuser or currently undergoing treatment for alcohol and/or drug abuse;
- Is involved with current or pending litigation regarding a spinal condition;
- Has received drugs that may interfere with bone metabolism within two weeks prior to the planned date of spinal surgery (e.g., steroids or methotrexate), excluding routine perioperative anti-inflammatory drugs;
- Has a history of an endocrine or metabolic disorder known to affect osteogenesis (e.g., Paget's Disease, renal osteodystrophy, Ehlers-Danlos Syndrome, or osteogenesis imperfecta);
- Has a condition that requires postoperative medications that interfere with the stability of the implant, such as steroids. (This does not include low-dose aspirin for prophylactic anticoagulation and routine perioperative anti-inflammatory drugs);
- Has received treatment with an investigational therapy within 28 days prior to implantation surgery or such treatment is planned during the 16 weeks following implantation.

NOTE: If a patient does not meet the entry criteria during the initial enrollment, the patient should not be re-evaluated for entry into the study at a later time.

3.2.4. STUDY DESIGN

3.2.4.1. OVERALL STUDY DESIGN

Each site will be asked to target a minimum of 10 subjects depending on patient availability. Each US site will not be permitted to enroll more than 25 subjects (includes one training subject). 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 two-level Simplify Disc clinical study prior to their first implantation procedure.

Subjects will be considered enrolled in the study for the purposes of an intent-to-treat analysis, only after they have been treated as determined by the recording of 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 with a time of incision will be included in the "intent to treat" analysis set, 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 techniques to ensure reproducibility.

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

3.2.4.2. CONTROL GROUP

The proposed ACDF control group is from [redacted] multi-center, prospective, randomized, non-inferiority clinical trial [redacted] completed in the US. This study compared [redacted] to conventional ACDF for treatment of subjects with two-level DDD who are symptomatic at two contiguous levels from C3 to C7 that is unresponsive to conservative management. Subjects were treated between [redacted] and [redacted]. A total of [redacted] subjects were treated at [redacted] investigational sites, [redacted] subjects in the investigational [redacted] treatment group, and 188 subjects in the

control group (all randomized in a 1:1 ratio). 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 control treatment was a bi-level fusion procedure with allograft (cortical ring) bone and [redacted]. The use of autograft bone from the iliac crest, cancellous bone paste, or DBM with the allograft bone was not permitted in the control treatment. Closure will be the same for the control group and the investigational device. There have been no important changes in the surgical methods pertaining to conventional ACDF.

3.2.4.3. 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/hospital discharge, and post-operatively at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 4 weeks), 12 months (± 2 months), 24 months (± 2 months), 36 months (± 2 months) and other annual visits (± 3 months) thereafter until the last subject enrolled has completed the 24-month evaluation.

3.2.5. STUDY PROCEDURES

3.2.5.1. 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 Institutional Review Board (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.

3.2.5.2. 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
- Radiographic core lab evaluations;
- Dysphagia Handicap Index[13];
- Study related medical history and physical examination;
- DXA (if indicated as described in Section 3.2.3.3);
- NDI assessment;
- SF-36 Health Survey;
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);
- Neurologic evaluation;
- Gait assessment;
- Work status;
- Foraminal compression test;
- Study related medication history and
- Preoperative Patient Survey (medication and work status).

All pre-treatment measurements must be done within 6 months prior to surgery.

The neurologic evaluation will include a motor and sensory assessment and reflex responses. Reflexes that are hypo-reflexic will be considered as normal. Gait abnormality will be assessed.

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

For the purposes of this clinical study, all medications will be recorded preoperatively but only medication taken for neck/arm pain including the class of medication, i.e. non-narcotic, narcotic (strong and weak), and muscle relaxant, will be collected postoperatively.

3.2.5.3. TREATMENT PROCEDURES AND EVALUATIONS

The surgeon will use a standard anterior cervical approach, known as the Smith-Robinson[14] procedure for anterior approach, to the cervical spine. Details of the Smith-Robinson procedure are contained in the Investigator and Study Manuals**.** The diseased discs will be completely removed using a standard technique, decompressing the anterior surface of the spinal canal. If the surgeon believes that the posterior longitudinal ligaments are hypertrophic, ossified, or compressing a neurologic structure (e.g., nerve root or spinal cord), the posterior longitudinal ligaments will be removed. If either of the Simplify Discs cannot be visualized during implantation, a contrast media may be used. The Simplify Discs will be inserted following the appropriate procedure.

3.2.5.3.1. Simplify Disc

The surgical technique for implantation of the two level Simplify Disc is described in the surgical technique manual.

3.2.5.3.2. ACDF CONTROL

The conventional two contiguous level ACDF was performed using cortical ring allograft and stabilization with [redacted]. The anterior cervical plate system was fixed into place according to standard technique. Closure will be the same for both the control and the Simplify Disc device groups.

[14] 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.

3.2.5.3.3. TREATMENT/HOSPITAL DISCHARGE EVALUATIONS

Treatment evaluations and data collection obtained during surgery and prior to hospital discharge will include:

- Levels treated;
- Length of surgery (skin-to-skin);
- Amount of blood loss;
- Length of hospital stay;
- AP and lateral X-rays (plain films);
- Radiographic core lab evaluations;
- Neurologic evaluation;
- Adverse events as defined by Section 3.2.6.1 and Section 3.2.7 of this protocol.
- [redacted]

3.2.5.4. POST-TREATMENT EVALUATIONS AND DATA COLLECTION

3.2.5.4.1. POSTOPERATIVE CARE

Following completion of the procedure, subjects will receive treatment according to a standardized postoperative care protocol. The recommended postoperative regimen for study patients is as follows:

1. Avoid overhead lifting, heavy lifting, and repetitive neck bending for at least 60 days postoperatively.
2. Avoid high-impact/pounding exercising and/or athletic activity for at least 60 days postoperatively. Low impact/non-pounding exercising and/or athletic activity is permissible.
3. Avoid prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) and steroidal drugs. Low dose aspirin for prophylactic anticoagulation and the short-term postoperative use of anti-inflammatory medication are acceptable.

4. Postoperative bracing requirements will be left to the discretion of the investigators; however, information regarding the type of orthosis used and duration of use will be collected on postoperative CRFs.
5. Electrical bone growth stimulation should not be used for treatment of the cervical spine during the 24-month follow-up period.
6. Patients who are smokers should be encouraged not to smoke.
7. Unless not medically feasible, the use of NSAIDS in the investigational group is recommended for two weeks postoperatively.

3.2.5.4.2. FOLLOW-UP EVALUATIONS AND DATA COLLECTION

Follow-up evaluations at 6 weeks will include:

- AP and lateral X-rays (plain films);
- Flexion-extension X-rays (used to determine range of motion);
- Postoperative subject survey (medication and subject satisfaction);
- Physician perception of results
- Work status;
- Dysphagia Handicap Index;
- NDI assessment;
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);
- Foraminal compression test;
- Neurologic evaluation;
- Gait assessment;
- Study related medications;
- Adverse events as defined by Section 3.2.6.1 and Section 3.2.7 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;
- Postoperative subject survey (medication and satisfaction);
- Physician perception of results;
- Dysphagia Handicap Index;
- NDI assessment;
- SF-36 Health Survey (6 months);
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);
- Foraminal compression test;
- Neurologic evaluation;
- Gait assessment;
- Study related medications;
- Work status and
- Adverse events as defined by Section 3.2.6.1 and Section 3.2.7 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 for Investigational group (24 month);
- Radiographic core lab evaluations;
- Postoperative subject survey (medication and satisfaction);
- Dysphagia Handicap Index;
- NDI assessment;
- SF-36 Health Survey;
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);

- Foraminal compression test;
- Physician perception of results;
- Neurologic evaluation;
- Gait assessment;
- Study related medications;
- Work status;
- Adverse events as defined by Section 3.2.6.1 and Section 3.2.7 of this protocol and
- [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;
- Postoperative subject survey (medication and satisfaction)
- Dysphagia Handicap Index;
- NDI assessment;
- SF-36 Health Survey;
- Neck and arm pain questionnaires (neck, arm, left arm and right arm);
- Foraminal compression test;
- Physician perception of results;

- Neurologic evaluation;
- Gait assessment;
- Study related medications;
- Work status;
- Adverse events as defined by Section 3.2.6.1 and Section 3.2.7 of this protocol and.
- [redacted]

3.2.5.4.3. 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:

- Intervertebral Angle;
- Change in Intervertebral Angle;
- Horizontal Translational;
- Change in Horizontal Translational;
- Global Range of Motion;
- Change in Global Range of Motion;
- Disc Height (assessed by determining Functional Spinal Unit [FSU] height and by directly measuring height of disc space)
- Change in Disc Height;
- Disc Angle;
- Change in Disc Angle;
- Spondylolisthesis;
- Change in Spondylolisthesis;
- Device Condition;
- Device Bending;
- Device Breaking;
- Device Fracture;

- Device Subsidence (can also be derived with FSU Height);
- Device Migration;
- Device Protrusion;
- Radiolucency;
- Heterotopic Ossification;
- Bridging Bone;
- Maintenance of PreOp Motion;
- Osteophyte Formation;
- Endplate Sclerosis;
- Kellgren-Lawrence Adjacent Level Disc Degeneration;
- Facet Degeneration;
- Stenosis;
- Modic Changes;
- Cysts and
- Additional Observations.

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

3.2.5.4.4. [redacted]

[redacted]

- [redacted]
- [redacted]

3.2.5.4.5. 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. Missed patient evaluations after the point of withdrawal will not be considered protocol deviations.

Subjects may be withdrawn from a clinical study early due to withdrawal of Informed Consent, death, lost to follow-up, or Investigator medical decision. Each premature termination from the study must have the reason for their withdrawal from the study documented in both the source documents and on the applicable case report form.

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 either or both of the Simplify Discs removed will be followed, but follow-up subsequent to these events will be summarized separately, if the subject has not withdrawn consent.

3.2.5.5. DATA COLLECTION SUMMARY

Time Point	Pre-op[1]	Tx/ Discharge[2]	6 wks[3]	3 mo[3]	6 mo[3]	12 mo[3]	24 mo[3]	Post 24 mo[3]
Informed Consent	X							
DDD assessment (MRI, CT or X-ray)	X							
Medical History & Physical Examination	X							
DXA	X							
AP & Lateral X-rays	X	X	X	X	X	X	X	X
Flexion & Extension X-rays	X		X	X	X	X	X	X
Lateral bending X-rays	X				X	X	X	X
MRI (or CT at Pre-op only); Investigational group only at 24M	X						X	
Radiographic Core Lab Assessments	X	X	X	X	X	X	X	X
Preoperative Patient Survey	X							
Dysphagia Handicap Index	X		X	X	X	X	X	X
NDI	X		X	X	X	X	X	X
SF-36 Health Survey	X				X	X	X	X
Neck and Arm Pain Questionnaires	X		X	X	X	X	X	X
Foraminal Compression Test	X		X	X	X	X	X	X
Physician Perception of Results			X	X	X	X	X	X
Neurologic Exam	X	X	X	X	X	X	X	X
Gait Assessment	X		X	X	X	X	X	X
Medications	X		X	X	X	X	X	X
Work Status	X		X	X	X	X	X	X
Treatment Assessments		X						
Postoperative Subject Survey			X	X	X	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 3.2.3.3 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 may be taken up to 6 months prior to surgery; pre-op medications should include medications to the subject is currently taking at the time of the pre-treatment evaluation.
2. Surgery/discharge evaluations must be taken prior to hospital discharge.
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) and 24 months (± 2 months) and annually thereafter. The study visit window for 36 months is (± 2 months) visits post 36 months is ± 3 months.

3.2.6. STATISTICAL CONSIDERATIONS

3.2.6.1. PRIMARY ENDPOINT

The study hypothesis is that in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain or myelopathy due to abnormalities localized to the levels of the two contiguous disc spaces at two contiguous levels from C3 to C7 that is unresponsive to conservative management, the Month 24 composite clinical success (CCS) rate of the two-level Simplify Disc will be no worse than conventional two-level ACDF when success is evaluated at Month 24.

Individual success for both the investigational and control groups is defined as:

- Neck Disability Index (NDI) score improvement of at least 15 points from pre-operative;
- Maintenance or improvement in neurological status[15],[16];
- No serious adverse event classified as implant associated or implant/surgical procedure associated; and
- No additional surgical procedure classified as a "failure."

Overall success will be determined based on data collected during the initial 24 months of follow-up. Each element of the neurological study exam will be evaluated for maintenance or improvement.

All secondary index surgeries will be classified as failures.

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

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

16 Due to COVID-19, not all 24M visits (entire or portion) are able to occur in-person. If a 24M in-person visit does not occur, the 12M result will be carried forward to represent unavailable 24M results in the primary endpoint and subsequently adjudicated by the CEC.

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

3.2.6.2. 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 at two levels is no more than 0.10 smaller than the probability of two-level ACDF control patients achieving Month 24 CCS. This study will be considered a success if the 1-sided p-value for rejecting this null hypothesis is less or equal to than 0.05.

3.2.6.3. STUDY DESIGN

The 188 control subjects from [redacted] will be used to form a valid control group for determining the safety and effectiveness of the Simplify Disc device. Effectiveness comparisons will be performed using sub

classification through propensity score (PS) quintiles (Rosenbaum and Rubin, 1983)[17]. This approach 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 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, subjects 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 in the investigational group. The standard implementation of the PS sub classification including iterative 'trimming' of subjects from the extremes of the PS distributions for both the

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

investigational device and controls in order for the Imbens and Rubin 2015 PS model estimation validity criteria to be met and maximum internal validity of the statistical inference. In response to FDA concerns that trimming of investigational device patients can lead to challenges with regard to labeling, the heuristic described by Maislin and Rubin 2010 has been modified to force retention of all investigational device patients. While it is recognized that this may reduce internal validity of the inference, the modified heuristic maximizes external validity since the investigational device analysis set corresponds exactly to the indicated population. In general, trimming of control patients are allowed given the goal of creating a control population that is as similar as possible to the enrolled investigational device patients. We note, however, that it may not be possible to achieve the desired Rubin criteria while also retaining every investigational device participant due to bias introduced by lack of propensity score overlap which reflects lack of covariate balance. In the case that a final PS designed sample that excludes device participants is required, effectiveness results from non-selected investigational device patients will be summarized separately, compared to those selected for inclusion into a PS subclass, and evaluated in effectiveness sensitivity analyses with implications discussed in the clinical study reports submitted for regulatory review. No matter what, all investigational device patients will be included in safety analyses in order to maximize the external validity of the observed safety profile. Only the baseline data used in the PS design will be summarized for trimmed 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 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 will be done through easily interpretable graphical means.

Given the expected similarity of the populations from which the investigational and control groups will be obtained and the specificity of the clinical indication, it is expected that no more than 20% of the ACDF controls will require trimming. The sample size analysis described below accounts for up to 20% trimming of ACDF. It is assumed that no investigational device patients will be trimmed and so no adjustment for investigational device trimming is included in the sample size analysis. Should there be investigational device trimming, it is expected that the number of investigational device patients requiring trimming will be very small with no appreciable effect on statistical power.

We acknowledge that because the proposed propensity score design can only assess the comparability of the two groups after the prospective enrollment has been completed, there can be significant risk that in the end the data may not be comparable. The sample size determination accounts for up to 20% of the ACDF subjects to be trimmed in the iterative heuristic used to construct PS sub classes that meet Rubin's validity criteria. The risk of insufficient sample sizes due to more than 20% control group trimming can be mitigated by continuing enrollment into one the investigational device group should this be needed to obtain the required sample sizes for 80% power to reject the non-inferiority null hypothesis.

An evaluation of the variable collected in the [redacted] study indicate that all component variables necessary to formulate the relevant composite clinical endpoints will be available. Any differences in endpoint evaluation are due to the nature of the difference between artificial discs and fusion procedures. The components of the CCS will be evaluated in the same fashion for the ACDF control as they are to be evaluated for Simplify Disc enhancing comparability of results from the two studies. Although composite clinical success requires a threshold improvement in the Neck Disability Index (NDI), the "NDI is the oldest and most

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

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].

Similarly, an evaluation of the baseline variables collected in the [redacted] study indicate that a sufficiently rich set of common baseline covariates were collected in both studies. A key exception to this is the baseline pain instrument. The [redacted] study utilized a numerical rating scale while the Simplify study was originally designed to use a 100 mm VAS. In order to have comparability with regard to this key baseline covariate and for evaluations during the follow-up period, the Simplify study will now also utilize a numerical rating scale. The very small number of patients enrolled into the Simplify study evaluated with a baseline VAS will be included in the analysis with baseline VAS imputed as missing values as described below.

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 in Month 24 composite clinical with acceptably low bias.

At the conclusion of the PS sub-classification but prior to unblinding the statistician responsible for the PS analysis, results will be distributed to key stakeholder including model building process, summary of optimality criteria, and tabular and graphical summarizes of

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.

achieved covariate balance. This will include the use of a "Love Plot" (Ahmed et al 2006[28]) that compares balance before and after application of the PS sub-classification heuristic, adjusting for PS subclasses.

3.2.6.4. SAMPLE SIZE ANALYSIS

The current study is designed to demonstrate non-inferiority using a non-inferiority margin equal to -10.0% at a 1-sided type 1 error rate of α=0.05. Subclassification using propensity score (PS) quintiles will be used to minimize selection bias arising from the non-randomized device group comparison. Mantel-Haenszel stratified analyses accounting for PS subclass will utilized when testing the primary non-inferiority hypothesis. A total of 182 two-level investigational subjects will be enrolled and compared to two level ACDF control subjects. The pool of two level ACDF control subjects includes a sample size of N=188. The sample size analyses below demonstrate that these sample sizes are sufficient to test the primary non-inferiority hypothesis after accounting for loss-to-following and PS 'trimming' of controls during the observational design phase.

According to Table 28 contained in the [redacted] SSED, the overall success was achieved in [redacted] controls. Therefore, the control group Month 24 CCS probability was assumed to be 70%. The total control sample size reported in the SSED is N=188. Since selection into a PS sub class will be conducted without access to outcome data, it is assumed that 85% of the selected controls will have a complete Month 24 CCS endpoint. It is also assumed that up to 20% of the controls will be trimmed as part of the PS modeling process. Therefore, for purpose on initial sample size analysis, the control sample size is assumed to be N = 188 * .85 * .80 = 128.

It is noted that the 2-level [redacted] group experienced an [redacted] success rate. For the purpose of sample size analysis, it is assumed that the 2-level Simplify disc

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28 Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J* 2006; **27**(12): 1431-9.

group will have at least a small true superiority margin of 3.5%. That is, it was assumed that the true probability of Month 24 CCS for the investigational group is 75.0%. As noted above, the primary effectiveness hypothesis is non-inferiority with a non-inferiority margin of -0.10 to be tested using at one-sided α=0.05. With these assumptions, 154 investigational device patients are required for 80% statistical power as determined using industry standard software (nQuery Advisor 7.0 module PTE0U-1).

"When the sample sizes in the groups are 128 and 154, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 80% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, p_T - p_S, is -0.100 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 0.035 and the proportion in the standard group is 0.700."

To account for up to 15% loss-to-follow-up, the total enrolled investigational sample size will be N=182.

3.2.6.5. ANALYSIS SETS

The study contains two treatment arms with patients receiving either two-level Simplify Disc or two-level ACDF. The following subject groups or analysis sets will be used to complete the analysis of data.

- Intent-to-treat (ITT) analysis set: The ITT analysis set will include all enrolled patients in which treatment was attempted as defined by the recording of incision time and excluding training cases. Patients will be included according to their intended treatment device. Since the investigational and control treatments are to be performed at different institutions, it is not possible for subjects to receive the alternative treatment. Therefore, the ITT analysis set will be used in safety analyses.

- Primary Effectiveness (PE) analysis set: The PE analysis set includes all subjects in the ITT analysis set that are selected into a propensity score subclass. Primary effectiveness analyses will be conducted using the PE analysis set. Selection into a PS subclass is the observational study equivalent to being randomized. Intraoperative failures will be included in primary non-inferiority testing as composite clinical endpoint failures. Patients with no follow-up subsequent to surgery will be treated as having a missing primary composite clinical endpoint and will be handled according to the approaches outlined below.
- Per protocol (PP) analysis set: The PP analysis set will include patients in the PE analysis set that have no major protocol deviations including clinically significant deviations from inclusion or exclusion criteria. Secondary efficacy analyses will be performed using the PP analysis set.
- Training cases analysis set: Training case safety and effectiveness data will be summarized separately.
- Original Protocol (OP) analysis set: All patients enrolled in the original protocol prior to approval of the subject protocol with the [redacted] historical control will be analyzed separately to determine if they would meet the current patient enrollment criteria. OP safety and effectiveness will be summarized separately and compared to the ITT analysis set. Please note, due to the small sample size, these comparisons will lack statistical strength and will be provided for informational purposes only.

3.2.6.6. NON-INFERIORITY TESTING

The primary non-inferiority test will be conducted using a Mantel-Haenszel stratified analysis approach to pool over PS subclass specific estimated device group differences. If the one-sided p-value for non-inferiority is less than or equal to 0.05, it will be concluded that the two-level Simplify Disc is non-inferior to the two-level ACDF control. In addition to hypothesis testing, the lower bound of a one-sided 95% confidence for the true difference of the device group difference will be determined.

3.2.6.7. SUPERIORITY TESTING

If the non-inferiority study success criterion is met, superiority testing will be performed in the PE analysis set. It will be concluded that the two-level Simplify Disc is superior to the two-level ACDF control if the one-sided p-value for superiority is less than or equal to 0.025. By the closed testing principal there is no need for a multiplicity adjustment when testing superiority after rejecting the inferiority null hypothesis. Note that 1-sided α=0.025 is specified for testing of superiority rather than 0.05 in order to have more definitive evidence to support the stronger claim of superiority.

3.2.6.8. HANDLING OF MISSING DATA FOR PRIMARY CCS ENDPOINT

The first approach to be used to handle missing data for the primary CCS endpoint is to limit the expected amount of missing data through exceptional study conduct and management and this is the goal of all study personnel. However, some missing data from lost to follow-up is inevitable in these types of clinical trials. Moreover, it is known that some control patients were not evaluable for the primary Month 24 CCS endpoint.

The following two approaches will used in testing of the clinical non-inferiority hypotheses stated above.

1) Complete case analysis followed by tipping point sensitivity analysis (see below); and

2) Multiple imputation (MI) (see below).

The primary non-inferiority test will be conducted using the multiple imputation approach described below. The complete case analysis followed by tipping point analysis will be performed as a sensitivity analysis for the assumptions inherent in MI.

Multiple imputation (MI)[29] is a methodology used to address missing values due to LTF and possibly other reasons. The validity of MI depends on an untestable assumption known as

[29] Rubin DB and Schenker N. Multiple imputation in health-care databases: An overview and some applications. Statistics in Medicine 1991 10:585-598.

missing at random (MAR)[30] which is a much weaker assumption than missing completely at random (MCAR) which requires unconditional independence. Although MAR is likely to hold in many more situations than MCAR, in any given situation there is no way to confirm whether the assumption of MAR is tenable and consequently, whether or not the MI analysis produces valid inference. For this reason, a complete case analysis followed by a tipping point sensitivity analysis will be conducted in sensitivity analyses (see below). MI will be used to impute missing final NDI in patients otherwise evaluable for primary CCS. For each imputation, the composite endpoints would be constructed from the imputed NDI values and within randomly completed data sets, the device group difference and standard error is determined. For these imputations, the status of the other CCS components will be based on available data up to the point of loss-to-follow-up which is essentially a last-observation-carried forward approach. In this case, the patient's Month 24 secondary surgical intervention status, major device-related complication status, and neurological success status will be inferred from their Month 12 status. Imputations for NDI will be repeated 20 times to produce 20 randomly completed data sets. 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 as described in Rubin and Schenker 1991. The MI standard error will be used in the derivation of the p-value to test the non-inferiority hypothesis. MI analyses will be performed using SAS[31] Proc MI and MIANALYZE or their equivalent.

A complete case analysis followed by a tipping point analysis will be conducted to complement the primary MI approach in order to evaluate the robustness of statistical conclusions to the assumptions inherent in MI analyses. This includes the untestable assumption; namely, that the probability that a value is missing is independent from the value itself conditional on baseline values and clinical status up to the point. In a tipping point analysis, missing values in each group are separately assumed to be either successes or

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[30] Rubin DB Inference and missing data. Biometrika 1976, 63:581-592.

[31] SAS Institute, Cary NC.

failures. Treatment group differences will be computed based on all possible combinations of assigning success or failure to the primary overall success endpoint to the patients in the two groups. For example, one scenario will be that all missing two-level Simplify values are failures and all missing two-level ACDF values are successes. The next scenario would have one success and the remaining missing values as failure for two-level Simplify keeping all missing two-level ACDF as successes, and so forth. The 1-sided p-value for testing the primary non-inferiority hypotheses will be determined for each scenario. These results will be plotted using a dot plot with the number of missings assumed as failures for two-level Simplify on the x-axis and the number of missing assumed as failures for two-level ACDF on the Y-axis. The dots will be color coded to indicate whether or not the primary statistical conclusion changes under each individual scenario. If the fraction of scenarios in which the statistical conclusion changes is small, the primary results will have been shown to be robust against assumptions concerning missingness.

3.2.6.9. Handling of Missing Covariate Data For PS Analyses

The amount of missing baseline covariate to be used in the PS analysis is expected to be very small. This includes the missing numerical rating scores for a very small number of investigational device patients (~10) that were enrolled based on VAS pain scores. Prior to PS analysis, missing baseline covariates will be imputed using a single imputation based on multiple linear regression for continuous baseline covariates and multiple logistic regression for missing dichotomous baseline covariates.

3.2.6.10. Plans to Assess Site Poolability

Since different institutions are enrolling patients into the investigational and control groups, it is not possible to evaluate between site differences in relative efficacy. Therefore, analyses will focus on evaluating site variability in percentages of subjects achieving Month 24 CCS.

A random effects meta-analysis approach (DerSimonian and Laird[32]) will be used to evaluate whether there is more site variability that can be explained by within site sampling variability. Success rates will be transformed to stabilize variances to meet the normality assumptions inherent in this approach. Site specific transformed success rates are assumed to follow a normal distribution with mean μ and variance τ^2. The magnitude of site-to-site variability in the transformed success rates will be quantified using the I^2 statistics (Higgins et al 2004[33]). 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 in treatment effect is important will involve the comparison of the observed I^2 value 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 to these analyses. If significant site variability is observed, sites will be removed one-at-time to identify site(s) contributing significant treatment effect heterogeneity and the identified site subjected to additional analyses aimed at understanding the cause of this heterogeneity.

3.2.6.11. [redacted]

[redacted]

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

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

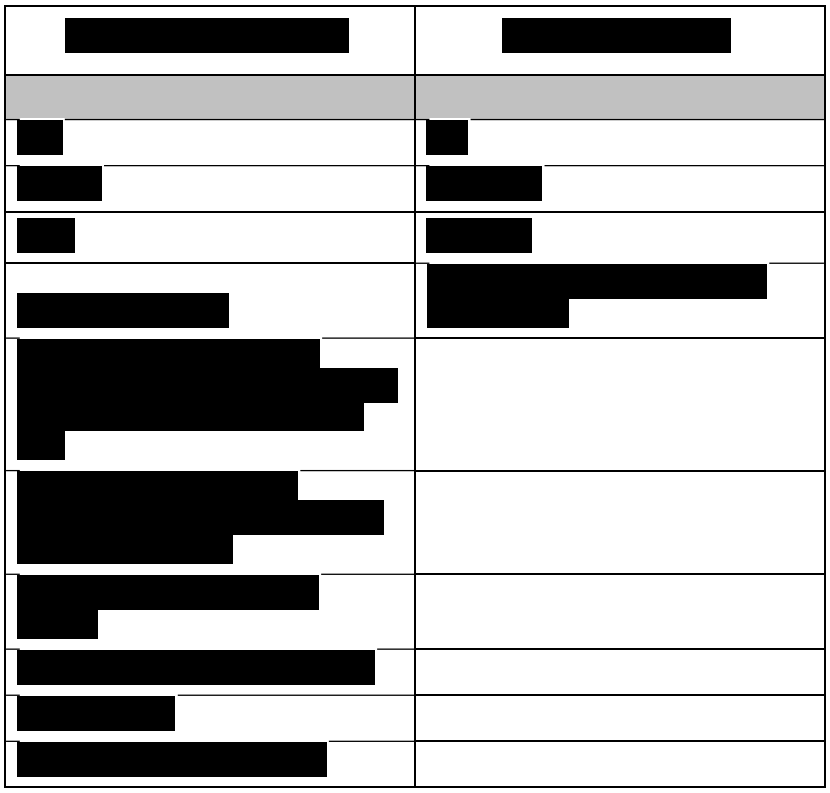
3.2.6.12. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]



3.2.6.13. SECONDARY EFFECTIVENESS ENDPOINTS

Secondary endpoints include:

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

Success is predicated on maintenance or improvement in neck and arm pain status according to the following equation:

Preoperative Score - Postoperative Score > 0

(Score = pain intensity + pain duration).

- 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.[35]

- Time to recovery (time to first 15-point NDI improvement).
- Disc height (FSU Height) at each post-operative time point compared to baseline (6 weeks). Both levels have to be a disc height success to claim success for overall disc height. Disc height success for each level is based on either the anterior or posterior measurements meet the following criterions:

  Postoperative Height – 6 Week Postoperative Height ≥ -2mm

- Adjacent level deterioration at 24 months compared to baseline for the Investigational group.
- Displacement or migration of the device for the Investigational group; only changes of > 3 mm will be considered significant due to the margin of error in radiographic determination of displacement distances.
- Return to work status postoperative.
- Subject satisfaction and perceived effect at each applicable postoperative timepoint. Success for each satisfaction question (three) will be defined as either a "Definitely True" or "Mostly True" response. Success for the perceived effect will be defined as either a "Completely Recovered," "Much Improved," or "Slightly Improved" response.

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[35] Hacker *et al., supra* note 7.

- Health Survey (SF-36) at each applicable postoperative time point compared to baseline. Success will be expressed in terms of the PCS (physical component summary) and MCS (mental component summary) scores and will be defined as a maintenance or improvement in status postoperatively as compared to the preoperative condition. To be classified as a success for each component summary, the following criteria must be met:

  PCSPostop - PCSPreop ≥0

  MCSPostop - MCSPreop ≥0
- Dysphagia Handicap Index (DHI scale) at each applicable postoperative time point compared to baseline for the Investigational group.
- Facet deterioration at 24 months compared to baseline for the Investigational group.
- Adjacent Level Motion (Stability) will be compared at each applicable postoperative time point to baseline.
- Results at each applicable postoperative time point will also be categorized by the physician's perception of the subject's condition (excellent, good, fair, or poor).
- Gait assessment at each applicable time point compared to baseline. This will be based on Nurick's classification. Success will be defined as maintenance or improvement in the postoperative status as compared to the preoperative condition:

  Preoperative Score – Postoperative Score ≥0

3.2.6.14. OTHER OUTCOMES

Other outcomes to be measured include:

- Duration of hospitalization;
- Blood loss;
- Operative time (skin incision to skin closure);
- In vivo endplate thickness analysis will be completed on a consecutive series of the first 25 subject who complete the 24 month follow up visit.

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.

Subgroup Analyses

Primary and secondary effectiveness endpoints will be evaluated in subgroups defined by stratifying the primary effectiveness analysis set. Safety endpoints will be evaluated in subgroups defined by stratifying the safety analysis set. Subgroups to be evaluated will include, but not limited to:

Gender (Male vs. Female)

Age (Median cut point, ≥ 55 and < 65 years)

Height (Median cut-point)

Weight (Median cut-point)

BMI (Median cut-point)

Comorbidities

3.2.6.15. ANALYSIS OF ADVERSE EVENTS

This section summarizes statistical analysis plans for adverse event endpoints. The following section provides details regarding safety assessments including definitions and procedures.

The safety analysis set will be the ITT analysis set which includes all enrolled patients for which treatment was initiated as defined as a recording of an incision time. To enhance comparability when comparing safety profiles, only controls selected into a PS subclass will be included in primary safety analyses. Assessment of the safety of the investigational

implant will include an evaluation of the incidence and severity of complications and adverse reactions associated with the treatment in the safety analysis set.

Adverse event rates will be summarized by type of AE and for specific AEs in two ways: 1) per patient incidence of specific AEs and classes of AEs and 2) by event, summarizing event counts by visit interval over time and accordance with FDA Guidance (CDRH 2004)[36]. Device and procedure-related events will be summarized by severity and relatedness. Event listings will be provided that include details such as relatedness, severity, onset and resolution status will be provided for all events and relevant subsets of events such as serious events and related events. The summary tables will indicate the type of adverse event, the total number of such events, and the number and the percentage of patients affected in each treatment group ("subject wise evaluation") and also stratified by relation to device and severity. Data of drop-outs will not be presented separately, but possible bias will be discussed in the final report.

In addition to summary tables, the following AE listings will be constructed:

- AE Listing 1 All AEs Sorted by Device and Event Type
- AE Listing 2 All AEs Sorted by Device and Patient
- AE Listing 3 Unanticipated Adverse Device Effects
- AE Listing 4 Serious AEs
- AE Listing 5 Severe AEs
- AE Listing 6 Device Related AEs
- AE Listing 7 Serious Related AEs
- AE Listing 8 Severe Related AEs
- AE Listing 9 Procedure Related AEs
- AE Listing 10 Other AEs
- AE Listing 11 AEs among patients discontinued early
- AE Listing 12 AEs among patients who died

3.2.7. SAFETY ASSESSMENT

3.2.7.1. ADVERSE EVENTS

An adverse event is defined as any clinically adverse sign, symptom, syndrome, or illness that occurs or worsens during the operative and postoperative periods of the trial, regardless of causality, that is not otherwise being measured in the trial. This does not necessarily include immediate postoperative sequelae (such as chills, sore throat, nausea, vomiting, constipation, short-term fever unrelated to infection, straight catheterization, pain or burning during urination, etc.), unless it prolongs hospitalization or, in the opinion of the investigator, should be reported. Adverse events, whether or not device related, must be reported on the appropriate case report form. Any adverse event that occurred prior to treatment with the medical device will be documented in the patient's pre-operative medical history. Only adverse events which are new or have worsened during the course of this study will be evaluated in the safety assessment.

3.2.7.2. SERIOUS ADVERSE EVENTS (SAE)

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,

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4. Resulted in subject disability or permanent damage or required intervention to prevent permanent impairment/damage.

3.2.7.3. Unanticipated Adverse Device Effects (UADE)

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.

3.2.7.4. Adverse Event Recording

Adverse event information will be collected on all subjects. All adverse events must be reported on the Adverse Event Form.

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

The investigator should pay particular attention to the patient's postoperative neurological evaluations. It is important that any new, significant neurological deficits be reported as an AE.

In the event that a patient experiences an AE involving tumor formation, the investigator should provide a pathology report describing the location of the tumor; the histopathology of the tumor; other comorbid medical diagnosis; and the age of onset, gender, and ethnicity of the patient. Any information regarding the patient's family history of cancer should also be provided, if available.

3.2.7.5. Adverse Event and Unanticipated Adverse Device Effect Reporting

At each subject encounter, the investigator will determine if there has been an AE since the last encounter and if any previous AE's are ongoing or have resolved. Serious Adverse Events and Unanticipated Adverse Device Effects must be reported to the Sponsor and to the

approving IRB, if required, as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event. All SAEs have to be reported, whether or not they are considered casually related to the investigational medical device.

All SAEs that are related to the investigational medical device will be subject to expedited reporting. The Sponsor or site should inform IRB about SAEs associated with the use of the device, per local requirements.

3.2.7.6. Clinical Events Committee

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

The CEC may determine neurologic status has declined at 24 months compared to baseline based on changes including:

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

The CEC will also review all UADEs. Adverse events will be classified by the CEC based on seriousness, relationship to device and procedure, and severity. The CEC will also adjudicate protocol deviations. The CEC will consist of three spine surgeons who are not affiliated with the Sponsor or who are not participating in the study. The recommendations of the CEC and become part of the clinical trial data set.

3.2.7.7. Potential Relationship of Adverse Events

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

- Implant-associated: An AE for which there is a reasonable possibility that the event may have been caused primarily by the implant(s).

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

3.2.7.8. ASSESSMENT OF SEVERITY

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

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

3.3. RISK ANALYSIS

3.3.1. 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 or anaphylaxis
- Heart, pulmonary and vascular complications
    - Cardiac Event including myocardial infarction
    - Vascular complication including excessive bleeding or injury to blood vessels with potentially fatal bleeding
    - Edema
    - Soft tissue damage or fluid collections, including hematoma or seroma
    - Hypotension
    - Hypertension
    - Ischemia
    - Embolism including pulmonary embolism
    - Thrombosis
    - Thromboembolism
    - Thrombophlebitis
    - Stroke
    - Pneumonia
    - Atelectasis and other pulmonary complications
- 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
    - Skin or muscle sensitivity over incision which may cause skin breakdown or pain and irritation

- Gastrointestinal or urogenital complications
    - Ileus, bowel obstruction or other gastrointestinal complications
    - Nausea or vomiting
    - Difficulty with urination
    - Urinary tract infection
    - Incontinence
    - Bladder dysfuntion or other urogenital complications
    - Reproductive system complications

- Other
    - Systemic infection
    - Seizures or convulsions
    - Inability to resume activities of normal daily living
    - Injury to nerves, including nerve damage or paralysis, muscles, or organs
    - Pregnancy complications, including miscarriage or fetal birth defects
    - Pain
    - Psychological Illness
    - Memory loss, confusion, hallucination or other changes to mental status
    - Reflex Sympathetic Dystrophy (RSD)
    - Death

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

- Risks to neurological structures
    - Dural injury
    - Arachnoiditis
    - Compressive neuropathy
    - Neurologic deterioration, including injury to nerves or nerve roots associated with the spinal cord, spinal cord, resulting in:
        - pain, such as neck or arm pain
        - weakness,
        - paralysis,
        - altered reflexes,
        - numbness,
        - tingling, or
        - other changes in sensation (such as dysesthesias and paresthesias)
        - bowel/bladder dysfunction
    - Coordination abnormalities
    - Dysphasia
    - Gait disturbance
    - Headache
    - Otitis media
    - Tremors
    - Cerebrospinal fluid leakage
    - Cerebrospinal fistula
    - Reflex Sympathetic Dystrophy (RSD)
- Risks to spine structures
    - Heterotopic ossification
    - Development of disc degeneration or herniation at adjacent levels
    - Facet joint degeneration

  - Infection of the disc, bone, or surrounding soft tissue
  - Inflammatory conditions, such as discitis
  - Loss of disc height
  - Loss of anatomic sagittal plane curvature
  - Scarring
  - Soft tissue damage
  - Spinal instability
  - Spondylosis
  - Spondylolysis
  - Spondylolisthesis or vertebral listhesis
  - Spinal stenosis
  - Other injuries to surrounding structures of the spine including adjacent vertebrae
- Risks to structures of the neck
  - Airway obstruction
  - Dysphagia,
  - Sore throat
  - Recurrent aspiration
  - Dysphonia
  - Hoarseness
  - Laryngeal palsy
  - Vocal cord paralysis
  - Esophageal perforation
  - Pharyngeal perforation
  - Tracheal perforation
  - Vessel damage and/or rupture
  - External chylorrhea
  - Fistula
  - Lymphadenopathy or lymphatic vessel injury
  - Other injuries to organs and structures of the neck

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

- Device Position and Condition
  - Breakage,
  - Bending
  - Disassembly,
  - Loosening (early or late),
  - Malposition,
  - Subsidence/loss of disc height

  - Migration/displacement
  - Above issues can cause pain or injury to surrounding organs and structures, such as spinal cord, nerve roots or other neurologic structures that can result in pain, paralysis or numbness.
  - Above issues can cause blood vessel damage or erosion (could cause catastrophic or fatal bleeding)
- Anatomical difficulties during the surgery
- Technical difficulties implanting the device including trouble sizing the device and/or improper sizing of the device
- Adverse reaction or allergy to the device materials (PEEK, ceramic, titanium)
  - Autoimmune disease
  - Metallosis
  - Adverse tissue reaction (local or systemic)
  - Osteolysis or vertebral inflammation related to wear debris
  - Bone resorption
  - Tumor formation
  - Scarring or other symptoms, such as chronic inflammation
  - Above issues could lead to implant loosening or failure of the device
- 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 or bending
  - 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 levels (reoperation, revision, removal, supplemental fixation, and other spinal surgeries) as defined in Section 3.2.6.1.
- The need for additional surgery at the level above or below the treated spinal levels
- Vertebral fracture
- Failure of the device to improve symptoms or function
- Change in alignment of spine or loss of proper anatomic curvature, correction, height or reduction of the spine (including spondylolisthesis, change in lordosis or instability of the spine)
- The development of a new or recurrent spinal problem at the surgery levels, or the development of a new spinal problem at the levels above or below the treated spinal levels
  - Pain

- Neurological deterioration, including muscle weakness or paralysis, changes in sensation (including numbness, dysesthesias, or paresthesias), decreased reflexes, or loss of bowel and/or bladder control
- Development of new radiculopathy or myelopathy
- Heterotopic ossification
- Spontaneous fusion
- Degeneration of other parts of the spine including facet joint or adjacent discs

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.

3.3.2. 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 sites 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.

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

3.4. INVESTIGATOR TRAINING, RESPONSIBILITIES AND OBLIGATIONS

3.4.1. INVESTIGATOR TRAINING

The sponsor will provide appropriate training to each investigator prior to study initiation. Training will address topics including the surgical procedure, selection of appropriate implant sizes, instrumentation for implantation, indications for use of the device, contraindications, management of complications, and postoperative subject care.

The Sponsor will also 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 the Sponsor, and will address topics such as the labeling of the devices, the implantation instruments, and the selection of appropriate implant sizes.

3.4.2. INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that the investigation is conducted according to this protocol and following the Investigator Agreement. Prior to study participation, the

Investigator is required per 21CFR54 to describe any financial arrangements they have with the study Sponsor. This information is to be updated as appropriate for one year after study completion.

The Investigator is responsible for ensuring that Informed Consent is obtained from each study subject. The Investigator shall permit the device to be implanted only under his/her supervision. Upon completion or termination of this study, or at Sponsor's request, the Investigator shall return to the sponsor any remaining unused devices or otherwise dispose of the device as the Sponsor directs. The Principal Investigator at each site is responsible for the device accountability. The Study Coordinator, or Principal Investigator's designee, is responsible for maintaining the device accountability log, which will include tracking the receipt and return/disposition of the devices. At each monitoring visit, the study monitors will review and reconcile the log, the device inventory and the device shipment records.

3.5. DEVICE DESCRIPTION

The Simplify Disc is designed to be used for reconstruction of two contiguous discs from C3 to C7 following discectomy at two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with neck pain, or myelopathy that is unresponsive to conservative management. 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. Each superior/inferior endplate pair is specifically designed for each configuration (i.e. 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. The system is packed preassembled and placed as one unit, by means of the insertion instrument.

The Simplify Disc 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).

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 4 mm tall and bi-convex with a radius of R 7.7mm. When assembled, the maximum range of motion of the Simplify Disc (as designed, without anatomic constraints) is ±12° flexion-extension, ±12° lateral bending. The device is unconstrained in rotation.

3.6. STUDY MONITORING

3.6.1. 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 ethical principles of current Declaration of Helsinki as adopted by the World Medical Association Declaration of Helsinki, CPMP/ICH Note for Guidance on Good Clinical Practices as applied to medical device studies, the ISO 14155 Clinical Investigation of Medical Devices, FDA's IDE guidance documents, as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. §812.46, the National Statement, requirements of the TGA, and any requirements of relevant Commonwealth or state/territory laws. 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.

3.6.2. 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, 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 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 responsibilities.

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.

3.6.3. 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.

All CRF information should be traceable to source documents. Surveys completed by the patient will be considered source documents. Other records that will be considered source documents are hospital records, clinic charts, x-rays, CTs, MRIs and DEXA scans. Copies of source documents that may be collected by NuVasive include, but are not limited to: signed and dated patient informed consent documents (redacted); operative summaries; hospital discharge summaries/orders; any relevant progress notes pertaining to AEs, reoperations, or deaths; and autopsy reports. In cases where assessments (e.g., foraminal compression test, neurological examination) are not dictated in the patient's clinical charts or documented on source worksheets, these CRFs will also be considered source documents. Surveys collected by tablet (if used) do not require source documents.

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 3.2.6.1 and Section 3.2.7 of this protocol.

3.6.4. 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.

3.6.5. 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, including pre-study visits, on-site visits or final visit reports, submitted by a site monitor will be reviewed by the Director or Manager. The monitor will assume responsibility for any corrective action.

3.6.6. 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.

3.6.7. 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.

3.6.8. 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.

Results of the study will be analyzed per the Statistical Analysis Plan (SAP) after the completion of the study and publicly reported in the FDA's Summary of Safety Effectiveness Decision when the PMA review is complete. Clinical data will also be published on

clinicaltrials.gov, including any negative outcomes or any unanticipated termination of the study. Furthermore, study progress (e.g., all safety, effectiveness, and radiographic data) is reviewed annually and reported to FDA so that any untoward results will be identified early on and the study terminated if deemed necessary by the medical monitor.

3.7. 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.

3.8. INFORMED CONSENT

The final clinical Investigational Plan (CIP) including the final version of the subject Informed Consent must be approved or given a favorable opinion in writing by an Institutional Review Board (IRB) before enrollment of any subject into the investigation. The Clinical Investigator is responsible for informing the IRB of any amendments to the CIP, as per local requirements.

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 some time 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 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.

3.9. ETHICAL CONSIDERATIONS OF THE CLINICAL INVESTIGATION

The Investigation will be conducted in compliance with applicable regulatory requirements relating to the conduct of the Study.