Guidance for Industry and FDA Staff

Preparation and Review of Investigational Device Exemption Applications (IDEs) for Total Artificial Discs

Document issued on: April 11, 2008

For questions regarding this document contact Barbara Buch, MD at 240-276-3737 or via email at barbara.buch@fda.hhs.gov or contact Sergio de del Castillo at 240-276-3751 or via email at sergio.dedelcastillo@fda.hhs.gov.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Orthopedic Spinal Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device evaluation

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

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Contains Nonbinding Recommendations

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Guidance for Industry and FDA Staff

Preparation and Review of Investigational Device Exemption Applications (IDEs) for Total Artificial Discs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

A. Introduction

This document was developed to describe our recommendations for IDE applications for total artificial disc devices. It provides guidance for developers on the appropriate pre-clinical tests and clinical trial designs to adequately evaluate the safety of these devices as well as their effectiveness to relieve symptoms of spinal etiology and improve quality of life. This document makes additional recommendations and supplements "Guidance Document for the Preparation of IDEs for Spinal Systems" (i.e., Spinal Systems Guidance).[1]

The purpose of this document is to provide guidance to industry sponsors and FDA staff about important preclinical and clinical information, which should be presented in an Investigational Device Exemption (IDE) application for total intervertebral disc replacement systems (i.e., total artificial discs). FDA is issuing this document to help ensure consistency and understanding between FDA and sponsors when developing IDE submissions for total artificial discs. We hope this guidance will conserve FDA and industry resources and facilitate timely review.

This IDE guidance document is applicable only to total artificial discs. This guidance document is **not** applicable to other types of spinal systems that are designed to allow some degree of motion in the spine, such as spinal stabilization systems using pedicle screws or other flexible implants *without* fusion, disc nucleus replacements, partial intervertebral disc replacements, any spinal joint replacements (e.g., facet joint replacement), any other joint motion sparing or replacing implants, and combination products that may include biologic or

[1] http://www.fda.gov/cdrh/ode/87.html

pharmaceutical materials. Because of the complexity of such devices and design-specific issues, sponsors are encouraged to submit pre-IDE submissions to the Orthopedic Spine Devices Branch (OSDB) to facilitate discussion regarding the important preclinical and clinical information required for an IDE application. Please contact the OSDB Branch Chief for additional information regarding the pre-IDE submission process.

This guidance does not pertain to spinal implant devices that are intended for intervertebral body fusion, which may include cages, vertebral body replacement devices, or spinal vertebral body augmentation devices for vertebroplasty. For information about the preclinical testing FDA recommends for other spinal systems, please see the Spinal Systems Guidance,[2] "Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures,"[3] and "Class II Special Controls Guidance Document: Intervertebral Body Fusion Device.[4]

In this guidance, a spinal "system" is defined here as the complete implant configuration. A "component" is a single element in a system. "Construct" references are typically made when discussing testing. For the purposes of this guidance, "system" and "device" are used interchangeably.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

THE LEAST BURDENSOME APPROACH

The issues identified in this guidance document represent those that we believe need to be addressed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: www.fda.gov/cdrh/modact/leastburdensome.html.

B. Device Description

In accordance with 21 CFR 812.25, your investigational plan must include a device description, which should include the following:

[2] http://www.fda.gov/cdrh/ode/87.html
[3] http://www.fda.gov/cdrh/ode/guidance/1543.html
[4] http://www.fda.gov/cdrh/ode/guidance/1540.html

- the device's intended use and indications for use;
- supporting magnified sketches or photographs of the total artificial disc attached to a spinal model;
- a table that includes each component name and corresponding part number;
- a complete written description of the individual components, including how any components interconnect;
- complete mechanical drawings with all dimensions and tolerances of each individual component and, if applicable, of the total system;
- a list of all instruments unique to the implantation of the subject system and supporting magnified sketches or photographs of them; and
- identification of the materials from which the device components are manufactured and any voluntary material standards to which these materials conform.

C. Report of Prior Investigations

Please refer to the Report of Prior Investigations section of the spinal systems guidance on preparing reports of prior investigations. In addition to the information in the spinal system guidance, you must indicate whether all non-clinical tests comply with Good Laboratory Practices (GLP) (21 CFR Part 58). (21 CFR 812.27(b)(3)) Otherwise, we recommend you explain why you believe the GLP requirements do not apply.

1. Clinical Data

Please refer to Item 1 of the Report of Prior Investigations section of the spinal systems guidance for information about this section.

A description of how the prior investigations have influenced subsequent changes in device design, patient selection and/or surgical technique and instrumentation should be included within clinical data reports, where applicable. (21 CFR 812.27(a))

Refer to the "Clinical Data Presentations for Orthopedic Device Applications" (Clinical Data Presentations Guidance)[5] for detailed descriptions of and sample tables for information concerning the items requested in this section.

2. Animal Data

Animal data used to establish the relative safety of your total artificial disc prior to initiating human clinical studies must also be included. (21 CFR 812.27(a)) Reasons for conducting animal studies could include:

- providing proof of concept;
- evaluating different design concepts, surgical instrumentation, or technique;

[5] http://www.fda.gov/cdrh/ode/guidance/1542.html

- identifying failure mechanisms;
- conducting functional studies (such as maintenance of motion and/or disc height without fusion or subsidence);
- addressing biologic response to particle and substrate materials; and
- assessing biocompatibility or toxicity.

In accordance with 21 CFR 812.27(a), you must include complete reports of any animal testing conducted on the device or its components, whether adverse or supportive, that are relevant to the evaluation of the safety or effectiveness of your system. The animal report must specify the purpose of the study and provide any supporting pathological, histological, and radiological evaluations. The animal report should also include an executive summary of the evaluation by a pathologist.[6] If testing was not done on the final, sterilized version of the system included in the IDE, describe the differences between that system and the version of the system used in your animal studies, and explain why you consider the testing and the results to be meaningful.

Your report of any animal testing should include:

- identification of the animal model and a rationale for the choice of animal model (e.g., relevance to human anatomy or disease);
- identification of the device components or materials (e.g., particles) used in the study and a rationale for why these were selected;
- the evaluation timepoints of the study and a rationale for choosing these timepoints;
- the number of animals evaluated at each timepoint and rationale for the number of animals chosen;
- identification of the test control;
- the results; and
- a discussion of the results in terms of the expected *in vivo* and clinical behavior of the device.

We recognize that choosing and validating an animal model may be difficult because there is no perfect model. Many animal studies have involved sheep, goats, primates, dogs, or kangaroos. In choosing an animal model for evaluating your device or system, you should ensure the model you select addresses the anatomy, physiology, biomechanics, and *in vivo* loads expected in clinical use. Each animal model should be appropriate to the purpose of the study.

[6] Cunningham BW, Orbegoso CM, Dmitriev AE, Hallab NJ, Sefter JC, and PC McAfee. The effect of titanium particulate on development and maintenance of a posterolateral spinal arthrodesis: an in vivo rabbit model. *Spine* 15: 1971-1981, 2002.

Functional Animal Study

For functional animal testing, we recommend that you perform all testing on sterilized components of the final device design. You should use a control for your functional animal testing to establish a frame of reference for the performance of your device and materials.

The functional animal model should reflect the intended use of the device. In particular, your test model and the levels of implantation in the animals should reflect the intended use of your device.

Particulate Animal Study

If the wear particles of any material in your device or system have not been comprehensively evaluated in the spine or at the indicated spinal level, FDA may recommend you conduct a study using a small animal model (e.g., rabbit). The objective of this study is to evaluate the local and systemic responses (e.g., biocompatibility, neurologic response, tissue response, and toxicity) to the wear debris.

The wear particles used in the study should represent the size, shape, amount, and chemical composition of those expected from *in vivo* use (i.e., representative of particles generated from durability and/or wear testing). Regardless of the amount of wear debris generated from bench-top testing, one group of animals should receive a sufficient dose so that particles can be located during histologic analysis. If wear particles cannot be identified and located, it may not be possible to draw conclusions about either particle transport or the local tissue reaction to particles from your device. We recommend 10 million particles for the high-dose group, although a larger amount may be necessary depending on particle size and composition. The histology results should account for the total amount of wear particles injected into the animal. For instance, if the particulates are injected into the lumbar spine, these particles should be observed at the injection site and/or in other parts of the body.

FDA recommends you document physical and neurological observations throughout the study. Animals should be sacrificed at 3 and 6 month time points, though longer time points might be needed depending on the material or device. You should harvest three (3) samples from three (3) different points of each organ/tissue evaluated in the following areas: spinal region, paraspinal region, dura, and local lymph nodes. Depending on the materials and the level the implant is indicated, FDA may recommend you evaluate additional tissues or organs such as spleen, kidneys, heart, liver, lung, and pancreas. An independent toxicologist should harvest all samples and analyze the pathological slides generated from the samples.

References to animal studies in the literature may be appropriate for evaluating the biological response to wear particles. If you cite the literature to support the biological response of your device, explain how the particles in the literature studies are representative of the particles expected from *in vivo* use of your device (e.g., representative of wear particles generated from durability and/or wear testing).

Cytokine Analysis
It may be appropriate to assess the potential for osteolysis by evaluating the cytokine response to wear debris. This testing may be accomplished through evaluation of the cytokine response during either a small animal particle implantation study or a functional animal study using, for example, the methods described by Cunningham et al.

3. Mechanical Data

FDA recommends you characterize your total artificial disc by preclinical mechanical testing. Alternatively, you may submit a rationale explaining why you believe such testing is not necessary to establish the relative safety of your device. Identification of appropriate mechanical testing influenced by the design, material, method of attachment to the spine, and target patient population must be included. (21 CFR 812.27(a)).

Your IDE must include complete reports for each test for all mechanical testing conducted on your system or its components, whether adverse or supportive, that is relevant to the evaluation of the safety or effectiveness of your total artificial disc. (21 CFR.278(a)) You must also include a comprehensive summary of all mechanical testing. (21 CFR812.(b)(3)) Each test report should include:

- an identification of the components that comprised the constructs or subconstructs tested;
- an identification of any test standard(s) to which the testing conforms, including identification and justification of all deviations from the test standard;
- the testing set-up;
- the testing procedures;
- a rationale supporting that the testing you conducted represents the worst case design;
- a rationale for the loading modes chosen (axial, bending, torsional, shear, etc.);
- the results, including the failure modes; and
- a discussion of the results in terms of the clinical requirements of the system (with reference to expected physiological loads and any supporting literature).

Unless you provide an adequate rationale, all mechanical testing should represent a worst case construct design of the total system and not mechanical testing of individual components. The device components that comprise the chosen worst case construct should be final, sterilized components. When there are differences between the system tested and your system, we recommend you explain how or why the results are relevant in establishing the relative safety of your system.

The test environment is dependent on the type of mechanical test being conducted. Some tests may be done under ambient conditions, while it may be necessary for other tests to

be conducted in a simulated physiologic solution (e.g., dynamic and wear debris testing). We recommend you include the rationale supporting the test environment you select for each type of mechanical testing.

All testing should be well-described and summarized with a clear, detailed rationale supporting that the testing and results are appropriate and clinically relevant.

Test standards are currently being developed by the American Society for Testing and Materials (ASTM) and the International Organization for Standardization (ISO) for static and dynamic characterization and wear assessment of total artificial discs. Two of these standards are published (ASTM Standard F2345-05: Standard Test Methods for Static and Dynamic Characterization of Spinal Artificial Discs; ASTM Standard F2423: Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses) and we recommend that you refer to these standards when devising a test protocol.[7]

Static and Dynamic Characterization

We recommend static and dynamic mechanical testing to characterize the device fully. For most artificial disc designs, we recommend you conduct axial compression and compression shear testing. Depending on the design of your device, FDA may recommend additional testing.

Static testing should involve six samples of a worst case construct. Fatigue testing should also involve six samples of the worst case construct to generate an Applied Force vs. Number of Cycles (AF/N) curve. Two or more samples should survive ten million cycles at a specific load. If the frequency of the dynamic testing exceeds 1-2 Hz, then you should explain the test frequency in terms of its effects on the device materials, test environment, test temperature, and machine accuracy. For example, if your device contains viscoelastic materials, such as ultra high molecular weight polyethylene (UHMWPE), your explanation should address how the chosen test frequency will affect these materials.

We recommend you conduct compression-shear testing using the device's maximum theoretical range of motion (ROM) in one or more of the directions of motion (e.g., full flexion/extension, full lateral bending). For any direction you did not test, we recommend you include the rationale that supports omitting that testing.

Many total artificial discs are unconstrained in rotation. Therefore, torsional testing may not be applicable. Nonetheless, a rationale for not providing torsional testing should be included.

Durability and Wear

We recommend you describe the theoretical range of motion (ROM) for your device in the various directions of motion (i.e., flexion, extension, lateral bending, axial

[7] http://www.fda.gov/cdr/ost/guidance/321.html

rotation) to adequately characterize the device. You should also describe the method through which you determined the ROM of your device.

The objective of the durability testing is to establish wear generation potential for the device as well as to possibly assess the stability. The durability or wear testing should involve cyclic loading that incorporates all directions of motion. This testing should be combined to incorporate all directions of motion into one test. Because most devices will be subjected to coupled motions (simultaneous motion about multiple axes) *in vivo*, FDA recommends you couple two or more of the motions during durability testing. We recommend subjecting each test specimen, regardless of test method used, to ten million cycles in all directions. If one or more motions are tested separately, you should vary the order of the motions among different test specimens to determine if there is any effect by the order of testing.

Because different areas of the spine have different ROMs, the parameters for the durability testing will depend on the intended locations (i.e., cervical or lumbar) for the device. The table below outlines test parameters FDA recommends for cervical and lumbar disc replacements. These parameters have been chosen based on testing that has been reported for various total artificial discs. If you chose different parameters, we recommend you provide a rationale supporting your choice, which may include evaluation of the device in simulated motion studies in cadaver spines. Because the motion of the device can depend on the level of implantation and the test methods employed, if you provide cadaver testing results, we recommend you explain how the results from cadaver testing represent worst case ROMs for your device.

Recommended Durability and Wear Test Parameters

Spinal Region	Flexion/ Extension (degrees)	Lateral Bending (degrees)	Axial Rotation (degrees)	Frequency (Hz)	Test Duration	Preload (N)
Cervical	±7.5	±6	±6	≤2	10 million cycles	100
Lumbar	±7.5	±6	±3	≤2		1200

You should perform all durability and wear testing in a physiological solution (e.g., bovine calf serum) and extract the wear debris from the test solution for characterization. Wear debris should be extracted from the solution using a filter with a pore size that allows collection of sub-micron particles. You should include a complete description of the debris extraction or filtering procedure. In addition, you should characterize the wear debris in terms of size distribution, shape, and chemical composition and retain the wear debris for future analysis. The methods described in ASTM F561 and ASTM F1877 or equivalent methods may be helpful in collecting and characterizing the wear debris.

FDA recommends you collect and characterize wear debris at least once every million cycles to determine if wear is increasing, decreasing, or remaining the same.

Some artificial disc devices are constrained (i.e., have limited ROMs) and alternative testing may be needed to evaluate the device at the upper limits of the device's ROMs. Testing at the upper limits of the ROMs should demonstrate that the device does not break down or generate excessive wear debris when the device reaches these limits.

Depending on the amount of data that you submit in an IDE for your device (e.g., animal data and/or clinical data collected outside the U.S.), durability and wear testing may not be necessary when you submit your IDE. In some cases, it may be possible to perform this testing concurrent with the clinical study and report the results in your IDE's annual reports and in your premarket approval (PMA) application. We recommend you contact the OSDB to discuss your plans to address the biological response to wear debris.

Subluxation and Expulsion

We recommend you assess the risk of subluxation of the superior components, inferior components, and any disc spacer used in the system. You should include a rationale to support that the testing conducted was adequate. The device should be tested in shear (or compression-shear) to expected *in vivo* loads that include an appropriate factor of safety. Depending on the design of the device, FDA may recommend you evaluate the risk of subluxation and expulsion in more than one loading direction.

Creep and Stress Relaxation

Because many disc replacement devices include viscoelastic materials that may be subject to creep and stress relaxation, we recommend you provide testing to assess this behavior and your rationale to support that the testing conducted was adequate. You should conduct creep testing under continuous compressive loading on the final, sterilized device to demonstrate that the disc height can be maintained over the life of the device. You should also include an accompanying hysteresis analysis.

Subsidence

We recommend you address the risk of subsidence of device components into the vertebral bodies through appropriate testing. You should include a rationale to support the test method used.

Kinematic Testing

We recommend you conduct a cadaver study evaluating the range of motion of the device *in vivo* compared to a normal spine. Please explain how the chosen number of cadaver specimens supports statistically significant results.

Device Migration

Sometimes, total artificial discs rely on press-fitting, ligamentotaxis, and rapid bony ingrowth into the endplates of the device to achieve adequate fixation. The rationales supporting your selection of tests and conclusions based on the test results should establish that the risk of device migration is minimal. Generally, we recommend

testing in an *in vivo* animal model to demonstrate that the surfaces of the endplates allow for rapid bone ingrowth and adequate fixation. We also recommend you provide complete test reports including a rationale for the test model selected, histology, characterization of ingrowth, and time to achieve ingrowth.

Durability of Coatings

We recommend you provide results from testing (e.g., shear, tension, abrasion) to characterize the stability and durability of any coatings on your device. You should also include a rationale explaining how your testing supports your conclusions. In addition, we recommend you describe the coatings in terms of materials, physical characteristics (e.g., thickness, morphology, pore size), and how the coating is applied to the device surface. Testing should include an evaluation of the device coatings under expected *in vivo* conditions to demonstrate that the coatings do not shear off. Methods described in ASTM F1044, F1147, F1160 and F1978 or equivalent methods may be appropriate for these tests. If the coating is not permanent, we recommend you describe any potential *in vivo* by-products, including:

- the degradation mechanism;
- the type of chemical reaction, if any; and
- whether the coating or any of its degradation products causes any damage to surrounding tissues.

We believe testing in a functional animal model with appropriate histological analysis may provide the best characterization and evaluation of any coating.

4. Biocompatibility Data

FDA may recommend biocompatibility testing depending on the materials used to comprise your system. Please refer to the guidance entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"[8] for additional information. We suggest you reference AAMI/ANSI/ISO 10993-1 or an equivalent method for a description of the type of information you should provide to address biocompatibility.

In addition, FDA may recommend animal data describing the response to the device material(s) in the spine (see Section C.2. - Animal Data).

If any of the total artificial disc components is manufactured from a polymer, we recommend that you provide the following information to characterize the final, sterilized material:

- information describing leachables
- average molecular weight

[8] http://www.fda.gov/cdrh/g951.html

- molecular weight distribution
- chemical and crystal structures
- percent of crystallinity
- degree of cross-linking of that polymer.

For any materials manufactured from polymers or that have the potential for leachables, we recommend that you provide an exhaustive extraction analysis of the final, sterilized device. Extractions should be done using both a polar (e.g., saline) and a non-polar solvent (e.g., hexane, acetonitrile). We recommend that you provide your rationale for the solvents you select for the extraction tests. The test report should include:

- the instrument sensitivities
- the type of solvent used
- the amount of leachables and impurities detected at part-per-billion (ppb) levels.

We recommend that you identify each leachable and impurity, whether detected qualitatively or quantitatively, examples of which include:

- any low molecular weight materials
- residual monomers
- solvent
- sulfur contents
- catalysts
- initiators
- lubricants.

5. Shelf Life Data

We recommend you evaluate all devices that can be affected by shelf life, sterilization, or aging (e.g., those with polymers or resorbable compounds). You should characterize the material of the final, sterilized device before and after aging to determine whether aging altered the material structure (e.g., molecular weight distribution, crystallinity, cross-linking) or the mechanical properties of the device. If shelf life or aging affects the component's material, you should perform the same mechanical testing of that component or system before and after aging.

D. Clinical Investigational Plan

The clinical studies submitted to support PMA applications should be designed and conducted in a manner that provides data that constitutes valid scientific evidence within the meaning of 21 CFR 860.7(c)(2). For FDA's recommendations about data presentation, please refer to the clinical data presentations guidance.

Much of the information provided in the spinal systems guidance is directly applicable to IDEs for total artificial discs. For the sake of brevity, only information specific to total artificial discs is presented in this guidance.

1. Choosing a Clinical Investigation Plan: Feasibility or Pilot Study vs. Pivotal Study

Unlike IDEs for many orthopedic implants, IDEs for total artificial discs often involve the introduction of new device designs or technologies or new clinical endpoints or assessments. Therefore, protocols for total artificial discs may vary in scope from a feasibility or pilot study to a pivotal study used to support the safety and effectiveness of the device for a future PMA application. These various types of studies are intended to address different questions and collect different types and amounts of safety and effectiveness information.

Your investigational plan must contain the elements listed in 21 CFR 812.25. In addition to the information in this section, please refer to Item 1 in the Investigational Plan section of the Spinal Systems Guidance for recommendations about information you should include in your investigational plan.

2. Purpose or Objective of the Protocol

The clinical protocol should begin with one or more clearly defined objectives and one or more clearly defined hypotheses. Please refer to Item 2 in the Investigational Plan section of the Spinal Systems Guidance for additional recommendations about information you should include in your protocol.

3. Study Design

FDA's regulations implementing section 513(a)(3) of the Food Drug and Cosmetics Act allow for FDA to determine whether other evidence submitted or otherwise available constitutes valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device. The implementing regulations also allow for FDA to determine whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use for PMA submissions based on data provided from IDE studies. 21 CFR 860.7(c)(2) identifies the following sources of valid scientific evidence:

- well-controlled investigations
- partially controlled studies
- studies and objective trials without matched controls
- well documented case histories conducted by qualified experts
- reports of significant human experience with a marketed device from which it can be fairly and responsibly be determined by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

While uncontrolled studies may be appropriate in some cases for feasibility studies, (e.g. to establish safety, to evaluate surgical technique, and/or endpoint, subject enrollment criteria and design appropriateness), when developing a future pivotal trial to demonstrate safety and effectiveness for artificial disc systems, FDA recommends that a multi-center, randomized, prospective, concurrently controlled clinical trial is appropriate. Such a study design offers the benefits of prospectively acquired data. It also provides advantages over other types of study designs by offering greater control of all parameters and by addressing some of the biases introduced by the other study designs.

Depending upon the specific situation, randomized concurrently controlled studies, non-randomized concurrently controlled studies, or historical-based studies may be appropriate so long as the chosen study design provides data that adequately supports the safety and effectiveness of the spinal system and minimizes inherent biases. Because artificial disc devices are novel and not currently in wide usage, it may be difficult to establish validated objective performance criteria in place of clinical outcomes. Regardless of the type of control you incorporate into your protocol, you should provide a complete description of the investigational and control groups as described below. You should also provide a rationale for your study design based on established scientifically sound clinical and statistical principles. Your rationale should describe how your protocol addresses inherent biases and accurately reflects the intended use of your device.

Please refer to Item 3 in the Investigational Plan section of the spinal systems guidance for additional recommendations about information you should include about your study design.

4. Choice of Control

Regardless of the type of control you plan to incorporate into the protocol, you should provide a complete description of the investigational and control groups. Please refer to Items 3.1 and 3.2 in the Investigational Plan section of the spinal systems guidance for additional recommendations about the choice of controls.

If you plan to use a control based on a literature control, i.e., a meta-analysis, we recommend you provide a rationale that supports pooling of patients into a single control cohort from published studies. You should demonstrate that any meta-analysis you provide is statistically valid. We encourage you to consult with the review branch about literature controls.

5. Inclusion Criteria

We recommend you provide a complete list of your inclusion criteria. Your inclusion criteria should adequately define the patient group you plan to investigate. The inclusion criteria appropriate for your study depend on your device, the target (disease) population, and the anatomic location of the disease process (i.e., cervical, lumbar). Please refer to

Item 4 in the Investigational Plan section of the spinal systems guidance for additional recommendations about inclusion criteria.

In addition to the inclusion criteria listed in the spinal systems guidance, we recommend the following additional criteria for total artificial disc studies:

- description of any restrictions regarding prior fusion, non-fusion, or adjacent level surgeries;
- description of the status of the adjacent spinal levels both radiographically and clinically (facet degeneration, disc height, osteophytes, etc.);
- scoliosis of less than 5 degrees;
- conditions of minimum bone density or quality for bony ingrowth or fixation;
- condition of instability or presence of stability defined by accepted parameters; and
- Minimum and maximum scores on baseline assessment scales.

Because of the inherent instability of the spine that may occur from the resection of primary or metastatic tumors, the use of some non-fusion spinal systems may not be appropriate in patients with spinal tumors. Information specific to tumors metastatic to the spine is described below in **17. Spinal Tumors**.

Studies involving patients with more than one level of fusion have typically demonstrated poorer outcomes than patients with single level of fusion. Since little is known about the treatment of multiple levels with motion sparing devices if you plan to include an evaluation of the use of your device at two or more levels, you should include a statistically significant sample size and a clinical relevance explanation that supports actual clinical use or accurately reflects the intended use of your device or target population. We also recommend you stratify the results from multiple level fusion separately from subjects with single level fusion. FDA also recommends that you limit any multiple fusion level study subjects to subjects with disease confined to one or two adjacent levels for study consistency.

The next sections address specific disease processes and anatomic spinal regions individually.

Degenerative Disc Disease (DDD)
Please refer to Items 4.1 (lumbar DDD) 4.6 (cervical DDD) in the Investigational Plan section of the spinal systems guidance for recommendations about including subjects with these conditions.

Scoliosis
Currently, diagnosis of pediatric congenital and adolescent scoliosis may be considered contraindications for total artificial discs. Axial, translational, and rotational forces of the spine in these patient populations may lead to early failure of

these types of devices. Please refer to Item 4.2 in the Investigational Plan section of the spinal systems guidance for recommendations about including subjects with these conditions.

Fractures Secondary to Trauma

FDA believes the principles of acute fracture treatment contradict allowing immediate motion if fracture healing is desired. You should provide a rationale supporting that the safe use of total artificial discs for the treatment of fractures secondary to trauma. Please refer to Item 4.3 in the spinal systems guidance for recommendations about including subjects with these conditions.

Spondylolisthesis

FDA believes that patients with moderate to severe (Myerding Grade II, III, IV and V) cases of spondylolisthesis, related instability or both are not appropriate candidates for total artificial discs. If you plan to include subjects with mild spondylolisthesis (Grade I), however, you should provide a rationale supporting that your device is safe for the treatment of Grade I spondylolisthesis. Please refer to Item 4.4 in the Investigational Plan section the spinal systems guidance for recommendations about including subjects with these conditions.

Revision Surgery for Pseudoarthrosis

FDA believes that it is appropriate to contraindicate total artificial discs for patients undergoing revision surgery for failed fusions used to previously treat pseudoarthrosis.

6. Exclusion Criteria

We recommend you provide a complete list of your exclusion criteria. Your exclusion criteria should adequately define the patient group you plan to investigate. Exclusion criteria may address a safety concern associated with a specific type of subject or exclude subjects who may negatively impact the study results or data analyses. Please refer to Item 5 in the Investigational Plan section of the spinal systems guidance for additional recommendations about exclusion criteria.

In addition to the exclusion criteria listed in the spinal systems guidance, we recommend the additional exclusion criteria discussed below.

Exclusion Criteria That Address Safety Concerns

Your exclusion criteria should address safety concerns by excluding subjects:

- with less than 5 mm of disc space remaining (We recommend, however, you identify subjects with a remaining disc space of 5-7 mm because it may be appropriate to modify this criterion based on the particular intended use or mechanics of your device.);

- with an additional spinal condition, other than the condition you plan to study, that may increase symptoms with additional motion or preclude insertion of the device (You should clearly define and list the excluded conditions.);

- on chronic medication affecting bone metabolism (steroids, osteoclast inhibitors, etc.);

- who have congenital stenosis or acquired degenerative stenosis with central, lateral, or combined central/lateral stenosis of the spinal canal or cord in whom treatment that destabilizes the spine or in whom increased motion may increase symptoms;

- with myelopathy (If you include subjects with myelopathy, you should provide a rationale supporting using your device design in these subjects and include a stratification of diagnostic groups);

- with severe spondylolisthesis of greater than 3mm (> Myerding Grade I);

- with severe degenerative disease, including facet degenerative arthrosis and adjacent level degeneration, which precludes safe implantation of the device without significant destabilization of any portion of the spinal column,

- with an anatomic deformity that inherently renders instability of the spine or facet joints

- who have undergone or will undergo any procedure that will leave the patient with deficient postoperative deficiency of the posterior elements or postoperative instability of the middle or anterior columns occurs, (e.g. with facet arthroplasty devices.); and

- with any other spinal deformity, instability, scoliosis, or kyphosis that precludes safe use of your device or other surgical intervention. (You should indicate and clearly define the range of radiographic measurements or clinical symptoms on which these diagnoses are made and which would exclude patients from your study; e.g., Cobb angle >10.)

Exclusion Criteria That Simplify or Clarify the Study Design

To help simplify the study design and to allow for interpretation of the study results, we recommend that you exclude subjects:

- with multiple involved levels in the spine; and
- with prior surgery at the surgical level you plan to study. (If you include subjects with prior surgery, however, we recommend you provide a rationale supporting pooling these subjects with subjects who have had no prior surgeries.)

7. Number of Investigators, Investigational Sites, and Subjects

We recommend you specify the number of investigators, investigational sites, and subjects. Please refer to Item 6 in the Investigational Plan section of the spinal systems guidance for additional recommendations about investigators, investigational sites, and subjects.

8. Study Duration and Follow-up Schedule

In order to properly assess all safety and primary effectiveness outcomes, your study should be designed to include 2 or more years of follow-up data. Please refer to Item 7 in the Investigational Plan section of the spinal systems guidance for additional recommendations.

Because novel spinal devices are often developed to address spinal disorders in younger, more active populations, we recommend that you design your study to address the possibility of a post approval study that may continue 5-10 years after implantation (i.e., studies FDA may require as a condition of the approval of your PMA application[9]). Therefore, we recommend that your IDE protocol include consent by all subjects to long term follow-up. In addition, you should enroll a sufficient initial number of subjects to submit long term data on a statistically significant number of subjects remaining after unexpected loss to follow-up.

9. Post-operative Regimen

We recommend you describe in detail any additional patient care procedures you plan to employ during the treatment period, e.g., surgery, rehabilitation, immobilization, weight bearing ambulation.

10. Safety and Effectiveness Endpoints

For the primary and secondary evaluation parameters that are measured at each timepoint, you should describe the specific parameter scales and methods of interpretation (i.e., success and failure criteria) along with your rationale and any validation of these measures. Please refer to Item 8 in the Investigational Plan section of the spinal systems guidance for additional recommendations.

Recommended endpoints for total artificial disc studies are summarized below, and are discussed in more detail in the sections that follow.

For lumbar spinal studies, primary evaluation parameters should include

- back and/or leg pain; and

[9] See also the guidance entitled "Procedures or Handling Post-Approval Studies Imposed by PMA Order: available at http://www.fda.gov/cdrh/osb/guidance/1561.html

- patient activities of daily living (ADL) function.

For cervical spinal studies, primary evaluation parameters should include:

- neck and arm pain; and
- patient ADL function.

FDA recommends you evaluate and document for each spinal level treated and the adjacent "normal" spinal levels, the clinical and radiographic:

- absence of device migration;
- absence of device failure;
- absence of fusion; and
- presence and amount of motion.

Depending on the design of your device, FDA may also recommend you evaluate as study endpoints:

- bone ingrowth;
- adequacy or stability of fixation; or
- other applicable parameters.

The choice of the following parameters as primary or secondary depends on the intended use. We recommend that you assess :

- neurologic status, which should be evaluated at each time point;
- disc height and vertebral height maintenance assessment;
- range of motion at the treated level;
- health-related quality of life;
- patient satisfaction; and
- return to work status.

The success criteria for each of the individual primary evaluation parameters will differ depending upon the design of the system, the patient population, and the goals of the treatment. (See Section **D.10 Study Success**)

Radiographic Success

For total artificial discs, the radiological assessments depend on the patient population and study goals. These assessments may include integrity of implant, maintenance of correction, maintenance of spinal segment stability, lack of migration, and maintenance or improvement of range of motion.

Radiographic evaluation should provide both safety information and effectiveness information about the investigational artificial disc device. Measurement of the same radiographic parameter can often provide both safety and effectiveness information.

Please refer to Item 8.1 in the Investigational Plan section of the spinal systems guidance for additional recommendations about radiographic endpoints.

Radiographic Safety Success

We recommend you provide evidence that the operative level and adjacent levels are stable and do not allow slippage in any direction *in situ*. We also recommend you document the degree of motion in each plane of potential motion for the operative and adjacent levels.

There are two distinct purposes for radiographic evaluation of implant location, evaluation of the initial placement, and evaluation of any subsequent migration of the device. You should determine and document whether the implant was successfully placed in the intended location at the time of surgery or immediately after the procedure. At each follow-up interval visit you should clearly assess and document the position of the device in relation to the initial implantation location and in relation to the ideally desired location. A radiographic report should include, but is not limited to, the position relative to the initial implantation, the position relative to the desired location, and the position during flexion and extension.

In addition to the above measurements, you should report your radiographic evaluation of the adjacent segment degeneration and general status of those segments.

FDA believes that for implant fixation to be considered stable, depending on the design of the device, the bone ingrowth area should exceed 75% of the bone to implant interface area intended for ingrowth.

Radiographic Effectiveness Success

For devices intended to maintain motion, we recommend you radiographically document maintained or improved motion. Radiographic motion as determined from flexion/extension plain radiographs, MRIs, or other specialized radiographic methods may be appropriate to estimate both preservation of motion at both the operative and at the adjacent levels. You should include an explanation of how motion is measured in your radiographic protocol.

Radiographic effectiveness endpoints that we recommend you evaluate include:

- successful preservation or improvement of motion (rotational, flexion, extension, lateral bending, translational, and angular motion or coupled motion of two or more of these) based on the physiology of the anatomic level being treated and levels adjacent to it; and the preoperative motion at the treated level as well as the design of your device;
- absence of evidence of bridging trabecular bone between the involved motion segments; and

For two-level treatment with the device, both levels should maintain motion to be considered a success.

Pain and Function

In addition to the information below, please refer to Item 8.2 in the Investigational Plan section of the spinal systems guidance for general recommendations regarding pain and function assessments.

We recommend you assess the subjects' severity and frequency of pain pre-operatively and post-operatively at specific follow-up times using a pain assessment score. You should attempt to distinguish pain due to problems with the spine, e.g., nerve root impingement, from the general pain that subjects might experience as the result of their overall medical condition, both at enrollment and post-operatively. You should also attempt to account for the type of analgesic medication the subject is using and how that may affect the pain assessment score.

Evaluation of function should focus on the post-operative ability of subjects to function independently, e.g., how does their ability to move around the house or neighborhood, dress themselves, or accomplish other daily activities compare to their pre-operative status. Evaluation may also include, depending on the population studied, the subjects' return to recreational activities. Return to work is also a parameter of interest in the working population.

When determining criteria for patient success for pain and function improvement, you should take into account the potential for a placebo effect[10,11] and use a consistent numerical value [such as 15/50 on the Oswestry Disability Index (ODI)] for patient success determination on each subjective assessment scale. You should clearly specify the clinically meaningful level of improvement, which may be different than the statistical level of improvement.

Because one of the purported mechanisms of pain relief is preservation of motion at the spinal level treated with a total artificial disc, you should include an analysis to evaluate any correlation between range of motion and pain and function outcomes (in your final analysis only).

Disc and Vertebral Height Assessment

In addition to the information below, please refer to Item 8.3 in the Investigational Plan section of the spinal systems guidance for additional recommendations about disc and vertebral height assessment.

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[10] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11;347(2):81-8. Summary for patients in: J Fam Pract. 2002 Oct;51(10):813.

[11] Harris W.H: Traumatic arthritis of the hip after dislocation and acetabular fractures: Treatment by mould arthroplasty J Bone Joint Surg p.737, 51-A, No.4, June 1969.

We recommend you measure disc heights adjacent to the operative level and follow the stability of disc height measurements over time. FDA does not necessarily recommend specific success criteria for this parameter, as these will depend on the intended use and expected performance of your device.

Health-Related Quality of Life

Please refer to Item 8.4 in the Investigational Plan section of the spinal systems guidance for FDA's recommendations about health related quality of life in these studies.

Safety Endpoints

Please refer to Item 9 in the Investigational Plan section of the spinal systems guidance for additional recommendations about safety evaluations.

We recommend you report and categorize as a supplemental fixation, any subsequent procedures related to the index level. This includes posterior fusion (whether removing the device or leaving it in place), decompression, facet rhizotomy, at the same, adjacent, or distant levels. Other surgical interventions should be reported separately.

We recommend you also include signs of myelopathy and gait disturbances as adverse events, particularly for cervical implant investigations. Cervical tension signs (Spurling's sign) and gait analysis may be appropriate assessments to determine the presence of these signs for cervical implants that allow semi-constrained or unconstrained range of motion.

Metal Ion Release

Published information for use of hip implants using metal-metal articulating surfaces has raised safety concerns, e.g., the risk of tumor formation, chromosomal aberrations, carcinogenesis potential in human patients.[12] Although retrieval analyses may be able to address some safety issues regarding metal-on-metal wear debris, FDA believes that metal ion release is an issue for devices implanted in the spine. FDA believes that all investigational protocols for metal-on-metal articulating devices intended to maintain motion in the any part of the human spine should include serum metal ion level analyses. You may wish to refer to the recommendations published in the literature to evaluate metal ion release levels in patients with metal-on-metal total artificial discs. Your investigation should evaluate the potential for the risk of tumor formation and carcinogenesis. Alternatively, you should provide a rationale with supporting references that either indicates that

[12] Doherty AT, Howell RT, Ellis LA, Bisbinas I, Learmonth ID, Newson R, Case CP. Increased chromosome translocations and aneuploidy in peripheral blood lymphocytes of patients having revision arthroplasty of the hip. J Bone Joint Surg Br. 2001; 83(7):1075-1081.

additional safety testing is not needed or that you have adequately addressed these with other testing.

11. Subject Success

Subject success may include a combination of objective and subjective criteria. You should take into account the placebo effect (typically 20-30%[13,14]) when determining the amount of clinically significant improvement that constitutes subject success in subjective self-administered assessment scales.

Subject success should be based on success in the:

- primary evaluation parameter of pain;
- primary evaluation parameter of function;
- absence of permanent neurological deficit;
- absence of secondary surgical intervention; and
- absence of serious adverse events.

Depending on the target population, study design, and study goals, it may be appropriate to include other assessments. You should count subjects who undergo certain secondary surgical interventions or experience serious adverse events or neurological deficits as failures of treatment. Improvement in pain and function should indicate clinically significant benefit, such as improvement of at least one subjective severity category to justify the risks of surgery (such as "marked disability to moderate disability," or "severe pain to moderate or mild pain").

Please refer to Item 10 in the Investigational Plan section of the spinal systems guidance for additional recommendations about subject success.

12. Study Success

You should also define study success for your clinical trial which takes into consideration the purpose of the treatment and comparison to a control group as well as the study goals (e.g., superiority or equivalency). All primary endpoint parameters, as well as safety information, should be accounted for in the definition of study success. You should clearly identify and justify the pre-specified allowable difference (delta) used to define differences between study arms.

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[13] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11;347(2):81-8. Summary for patients in: J Fam Pract. 2002 Oct;51(10):813.

[14] Harris W.H: Traumatic arthritis of the hip after dislocation and acetabular fractures: Treatment by mould arthroplasty J Bone Joint Surg p.737 , 51-A,No.4,June 1969.

Study success rates should be provided at each postoperative time point, but there will be particular focus on the results at the study primary endpoint (e.g., 2 years).

Please refer to Item 10 in the Investigational Plan section of the spinal systems guidance for additional recommendations about subject success.

13. Statistical Analyses and Data Presentations

We recommend you define the type of statistical analysis that you intend to perform before the study commences. Either Bayesian or frequentist statistical methods of analysis may be appropriate. Please see "Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices"[15] and "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials."[16]

If you switch methods after the study begins, we recommend you explain and model the reasons for the switch in order to avoid possible biases. We also recommend that you discuss with FDA any proposal to switch statistical methods before such a change is implemented.

We believe statistical methods are not an adequate substitute for completing your study (i.e., following patients through the entire study or for ending the IDE prematurely). You should provide statistical plans to account or adjust for missing data in your initial IDE.

Subgroup analyses may help you and FDA better understand the behavior of the subpopulations for which the device is indicated. Therefore, when you submit your PMA application, FDA may request further subgroup analyses to assess the safety and effectiveness of the investigational device in these subpopulations. However, post-hoc subgroup analyses should not be used to demonstrate effectiveness in the absence of a statistically and clinically significant effect in the total population.

In order to better assure that the study collects adequate data, your protocol should reflect the types of data presentations you plan to submit in your PMA application.

Please refer to Item 11 in the Investigational Plan section of the spinal systems guidance for additional recommendations about statistical analyses.

14. Patient Data Report Forms (Case Report Forms (CRF))

The CRFs that you develop should capture all relevant information from the protocol. Please refer to the spinal systems guidance for recommendations about CRFs. Original source documents (such as doctor's office notes, operative notes, radiographs or patient self-assessment questionnaires) must be consistent with the data recorded on these CRFs. (21 CFR 812.140(a))

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[15] http://www.fda.gov/cdrh/ode/odeot476.html
[16] http://www.fda.gov/cdrh/osb/guidance/1601.html

We also recommend your IDE include the forms and information described below.

The operative data form should document implant type, size, number used, and any intraoperative observations or adverse events. The adverse event form should identify all potential risks associated with implantation of your device. The form should also provide space for reporting of other adverse events, device related or not, and include spaces for the date, action taken, and date of resolution of the event. Where applicable, you should include the severity and association of the event to the device or procedure in the documentation.

We recommend you submit copies of each of the clinical evaluation scales or assessment questionnaires, e.g., Visual Analog Scale (VAS), Oswestry Disability Index, Short Form-36, patient satisfaction, work status.

We recommend you include a separate CRF for the independent radiographic review.

The study exit form should document the patient's reason for exiting the study, e.g., study completion, withdrawal, or loss to follow-up.

We recommend you include a special testing report form for reporting the results of any additional assessments specific to your investigational protocol (e.g., blood metal ion results).

Please refer to Items 12 in the Investigational Plan section of the spinal systems guidance for full details.

When using computerized or internet-based patient assessment forms, we recommend you follow the FDA guidance entitled "Computerized Systems Used in Clinical Trials."[17]

15. Risk Analysis

In accordance with 21 CFR 812.25(c), your IDE must include a description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition. You should include information adequate to determine that the benefits and knowledge to be gained outweigh the risks and potential complications the subjects may experience. In listing all of the potential risks, you should stratify the risks according to whether they are general to spinal surgery or specific to the device. Please refer to Item 13 in the Investigational Plan section of the spinal systems guidance for additional recommendations.

[17] http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm

Examples of potential risks related to device related complications include, but are not limited to:

- loss of function;
- fracture, subluxation, subsidence, or dislocation of the device;
- fracture of the adjacent bony structures;
- heterotopic ossification or segmental fusion (as relates to loss of motion);
- excessive wear or migration of the device or any of its components, even if such failure does not lead immediately to revision surgery or symptoms;
- facet degeneration at same level;
- adjacent segment degeneration;
- adjacent disc degeneration or intravertebral space height loss;
- infection at the level of the device;
- neurovascular compromise secondary to device impingement of these structures; and
- toxicity, carcinogenic potential or other biologic local or distant tissue or systemic effects due to by-products, debris (metal ion release) or breakdown products related to the device functioning in situ under physiologic conditions.

Examples of potential risks associated with the surgical approach include, but are not limited to:

- neurological complications, temporary and permanent
- vascular injury
- sympathetic disturbance
- painful or numb scar
- hematoma
- local drainage
- new pain or pain progression
- retrograde ejaculation
- dysphagia
- hoarseness/vocal cord dysfunction
- abdominal adhesions.

Examples of potential risks considered to be general complications of surgery include, but are not limited to:

- visceral dysfunction
- abdominal pain
- disturbance of urinary function

- urinary tract infection
- deep vein thrombosis
- phlebitis
- pulmonary embolism
- myocardial infarction
- cerebrovascular accident
- death.

16. Retrieval Study

We recommend you incorporate a plan to conduct retrieval analyses of explanted devices into your protocol, because the long term performance of total artificial discs is not well characterized. Please refer to Item 15 in the Investigational Plan section of the spinal systems guidance for additional recommendations about retrieval studies.

In addition to the recommendations about retrieval studies presented in the spinal systems guidance, we recommend you analyze a biopsy (within the limits of safety) of surrounding bony and soft (neurovascular) tissue for any inflammatory or other reaction to the device, and, where appropriate, metal ion or material debris content in surrounding tissue. Your protocol, labeling, and surgical technique manual should include specific instructions for the handling and returning explanted devices. Investigator training should also address this aspect of the investigation.

17. Spinal Tumors

Devices that maintain motion may not be appropriate for use in subjects with primary or metastatic neoplastic disease, due to the disease processes and adjunctive treatments that affect bone quality, spinal stability, and subject longevity. If you choose, however, to use a motion retaining device in patients with spinal neoplastic disease, you should provide a rationale explaining why such an investigation is scientifically sound and how the anticipated benefits to the subjects outweigh the risks to the subjects. Please refer to Item 16 in the Investigational Plan section of the spinal systems guidance for additional recommendations about devices intended to stabilize the spine when treating spinal tumors.

E. Monitoring

Your investigational plan must include your written procedures[18] for monitoring the investigation and the name and address of any monitor. (21 CFR 812.25(c)). Your monitor must be qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations. (21 CFR 812.43(d)). Please refer to the Monitoring section of the spinal systems guidance for additional

[18] These procedures should address the response to noncompliance, as described in 21 CFR 812.46.

recommendations about the monitoring procedures to be included in your IDE.

Your comprehensive monitoring plan must include the following:

- selecting qualified monitors (21 CFR 812.43(d));
- ensuring investigator adherence to the investigational plan and requirements (21 CFR 812.43(c)(4)); and
- ensuring investigator compliance in regard to record keeping and reporting (21 CFR 812.25(j)).

F. Labeling

In accordance with 21 CFR 812.20(b)(10), your IDE must include copies of all labeling[19] for the system. Please refer to the Labeling section of the spinal systems guidance for recommendations about labeling content.

In addition to the information recommended in the spinal systems guidance, your surgical technique manual for an artificial disc system should include:

- intended uses and indications;
- device description;
- contraindications;
- precautions;
- warnings; and
- potential risks associated with the subject system or a reference to the product insert for this information.

You should highlight or bold the text of instructions that affect the safety of use or are uncommon in current practice for emphasis.

FDA also recommends you include information in the surgical technique manual for explanting the device and revising the original procedure. In addition, your surgical technique manual should describe a salvage procedure alternative to revision or reimplantation.

G. Informed Consent

In accordance with 21 CFR 812.20(b)(11), your IDE must include copies of all forms and informational materials to be provided to the subjects to obtain informed consent. In accordance with 21 CFR Part 50, you must obtain and document the informed consent of the subject before the subject may enter the study. Your protocol should explain how you ensure that investigators properly obtain and document informed consent.

[19] Labeling for an investigational device must meet the requirements of 21 CFR 812.5.

In addition, the informed consent document must contain the elements described in 21 CFR 50.25. Please refer to the Informed Consent section of the spinal systems guidance for additional recommendations about informed consent documents.