



American Academy of
Orthopaedic Surgeons®

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March 10, 2005

Mark Melkerson
Deputy Director, DGRND
Food and Drug Administration
HFZ-140 Room 350D
9200 Corporate Boulevard
Rockville, MD 20850

Dear Mr. Melkerson:

The Orthopaedic Device Forum has completed a draft guidance on "*Preclinical and Clinical Trial Design for Cervical and Lumbar Disc Replacement Systems.*" Members of the Forum and the ad hoc group are pleased to assist the FDA in drafting proposed guidance documents that pertain to the practice of orthopaedic surgery so that they reflect current orthopaedic thought and practice.

The disc ad hoc group chairman sought out members who were non-conflicted. Two members were allowed to participate with conflicts of interest but their experience and expertise was deemed necessary to provide guidance to the development of the draft document. Appropriate disclosures were vetted with the entire ad hoc disc subcommittee.

We thank the FDA for receiving the submission of this draft guidance document. The Orthopaedic Device Forum will continue to assist the FDA in scientific matters of mutual interest. Thank you.

Sincerely,

John Kirkpatrick, MD JK

John Kirkpatrick, MD
Chair, Disc Ad Hoc Subcommittee

Bernard N. Stulberg, MD JK

Bernard N. Stulberg, MD
Chair, Orthopaedic Device Forum

2005D-0113



GUIDANCE DOCUMENT SUBMISSION

PROPOSED GUIDANCE DOCUMENT

FOR

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PRE-CLINICAL AND CLINICAL TRIAL DESIGN FOR CERVICAL AND LUMBAR DISC REPLACEMENT SYSTEMS

INTRODUCTION

The purpose of this document is to propose a standardized guideline for designing pre-clinical and clinical trials intended to measure the safety and efficacy of spinal disc replacements. A standardized guideline of study design will provide a least burdensome approach to designing, reviewing, and acceptance of study protocols for both sponsors and the FDA.

SCOPE

For the purpose of this document, a disc replacement is any device that is intended to replace a spinal disc, in part or in total, as a treatment for degenerative disc disease, segmental dysfunction, or as a substitute for inter-vertebral arthrodesis, where functional restoration and pain relief are the desired outcomes.

CONSIDERATIONS FOR DISC REPLACEMENT PRECLINICAL STUDIES

Goals

The broad goal of preclinical studies is to demonstrate that disc replacements maintain their mechanical and structural integrity under relevant simulated loads. Some designs will require shelf life studies and sterilization studies to demonstrate that material properties are maintained under various conditions.

General principles of total disc replacement arthroplasty as established in the literature should be followed. These general principles relevant to pre-clinical studies include:

- 1) Normal unconstrained physiologic motion under in vivo loads¹, aka kinematics preservation⁶
- 2) Independent anterior column support¹, also known as spacing preservation⁶
- 3) Biomechanics preservation⁶ including no load shifting to facets, wear resistance, no cold flow or delamination¹, 50 year expectancy, 100 million cycles⁶
- 4) Osteointegration (ingrowth)¹ or short term and long term implant-bone stability
- 5) Biocompatibility⁶

Biomechanical performance should be determined for disc replacements by standardized test methods where possible, and should demonstrate motion and load profiles with tests of longevity. Additional tests under physiologic load and motion should be performed to demonstrate wear and potential failure mechanisms. As consensus standards for disc

replacement testing are developed, those standards should replace literature methods listed below.

Motion characterization

Multidirectional flexibility testing of a single motion segment (or “functional spinal unit”) under unconstrained conditions using a cadaver model. Flexion/extension, lateral bending and axial rotation should be tested and compared to no implant and simulated fusion. Multisegmental flexibility testing should be done to compare the distribution of motion among segments both with and without a single segment disc prosthesis. Reporting should include both those segments with the disc replacement and those adjacent segments in the region.^{2,3,8} Analysis of facet loads with prosthesis in place should be performed.

Wear Testing

Cyclic loading of the device in a spine simulator, which replicates the approximate load and motion is expected for the region of the spine intended. Specific methods are currently being developed within ASTM International. Cyclic testing should be performed to device failure or a minimum* of 10 million cycles using physiologic coupled motion, with wear assessment and particle analysis at regular intervals^{6,7} with a minimum of 10 evenly spaced data points. This is dependent on the particular articulation interface materials. Testing should be conducted at 1 Hz in a temperature-controlled environment. Higher rates may be justified based upon specific designs but preservation of appropriate implant surface temperatures and the integrity of the fluid medium must be demonstrated. As a consensus standard is not yet approved, literature methods are used. Debris analysis should be performed to ASTM International standards⁷

The creation of a structural fatigue curve for the spinal construct may be considered in an attempt to define the product’s endurance limit.

*10 million cycles may be acceptable for full range of motion tests as this represents “significant bends” done clinically. Some testing methods not testing full range of motion may require up to 50 or 100 million cycles for adequate wear testing.

Host/Device Interactions

Local tissue cytokine analysis should be performed and have no difference from control tissue. There should be no local wear debris on histological analysis of local and reticuloendothelial tissues³. Any local debris and/or tissue reaction that is present should be clearly characterized and analyzed for potential adverse effects. Bone ingrowth or fixation area should be in excess of 30% of the bone/implant surface intended for ingrowth.¹ Adequate biocompatibility should be ensured by materials choices or adequate testing be done on new materials for biocompatibility.⁶ Standard biocompatibility tests (ISO10993), as well as additional biocompatibility testing of materials and composite materials at the sites of implantation should also be conducted to get a comprehensive assessment of biocompatibility.

CONSIDERATIONS FOR DISC REPLACEMENT CLINICAL STUDIES

Goals

The broad goal of clinical studies involving disc replacements is to generate safety and efficacy data for evaluating the use of disc replacements in treatment of damaged and diseased inter-vertebral discs. Safety is defined as reasonable assurance that benefits of the device outweigh the risks. This is evaluated on the basis of the number of adverse events relative to the number of subjects in the study and the apparent benefits derived from the experimental device. Efficacy is defined as reasonable assurance that, in a significant portion of the population, the use of the device will provide clinically significant results. This is evaluated on the basis of the extent to which pain is relieved, function is restored, and long-term goals are met.

Indications for Disc Replacement

The primary indication for disc replacement is discogenic pain in a patient who displays none of the contraindications for the procedure.

Contraindications for Disc Replacement

In addition to the general medical contraindications for any surgical procedure, a number of specific contraindications have been identified in the literature. These include

1. Central Spinal Stenosis
2. Lateral Recess Stenosis
3. Facet arthrosis
4. Spondylolysis
5. Spondylolisthesis (Some grade I spondylolisthesis may be appropriate for some designs.)
6. Herniated nucleus pulposus with radiculopathy
7. Scoliosis (curve magnitude greater than ten degrees)
8. Osteoporosis
9. Post-operative pseudarthrosis
10. Post-operative deficiency of posterior elements resulting in incompetence of the facet joints

General principles of total disc replacement arthroplasty as established in the literature should be followed. These general principles relevant to clinical studies include:

- 1) "Fail-safe" (failure does not risk other injury)⁶
- 2) Revisability or "reconstructability"⁶
- 3) Monitorable⁶

A minimum of 6 months nonoperative treatment should be attempted prior to disc replacement. Spinal fusion is reasonable comparison group. An additional comparison group could be those who would be considered surgical candidates, but continue nonoperative treatment after the six month time point.

Variables

No surgical options exist that both restore disc function and provide pain relief. Arthrodesis (fusion) may provide pain relief, but cannot restore joint function.

Decompression provides pain relief in those cases where neurologic impingement occurs but does not restore normal function to the motion segment.

Disc replacement devices have been developed and are undergoing clinical evaluations on function, safety, and effectiveness as potential treatment options. While much is known about spinal motion segment biomechanics, test methods, including directions of loading and loading protocols, remain somewhat controversial. The degree to which the loading and motion behavior of the disc replacement should match “normal,” and the definition of a control can be problematic. The use of multiple materials and some articulating surfaces require consideration of biocompatibility, wear, degradation and shelf life of these implants. In the context of the US regulatory approval process, clinical safety and efficacy of new disc replacement devices are best established through comparison with fusion results, using FDA-approved constructs if internal fixation is required.

Clinical comparison should take place within the context of standardized measures for safety and efficacy, including at a minimum: complication prevalence, standardized outcomes measures (such as Oswestry Disability Index), revision prevalence, and radiographic analysis.

A. Complication Prevalence

The complication prevalence is a measure of safety and is defined as the number of device and surgically related complications divided by the number of patients. All complications must be recorded, but only those considered clinically significant and related directly to the disc replacement should be included in the calculation. The excluded complications should be reported, however.

Examples of device complications that would be included:

- Loss of function as might occur through subluxation, subsidence, or dislocation of the disc any time post-operatively.
- Heterotopic Ossification (as relates to loss of motion)¹⁰
- Excessive wear, migration, or breakage of any component of the disc replacement, even if such failure does not lead immediately to revision surgery or symptoms.
- Facet degeneration at same level¹²
- Adjacent Segment degeneration¹² (V1)
- Infections of the device (for comparison to fusion)

Examples of approach complications to be reported (for comparison to fusion) include⁴

Neurological complications, temporary and permanent
Vascular injury
Sympathetic disturbance
Painful or numb scar
Hematoma

New pain or pain progression
Retrograde ejaculation Dysphagia
Hoarseness/vocal cord dysfunction

Examples of complications to be reported but considered general complications of surgery⁴

Visceral dysfunction
Abdominal pain
Micturition disturbance
Urinary tract infection
Deep vein thrombosis
Phlebitis
Pulmonary embolism
Death

B. Standardized spinal outcomes measures

One or more outcomes measures relevant to the region of the spine and even some systemic outcome measures should be used. The Oswestry Disability Index provides one example of a relevant measure for the lumbar spine^{8,9} and the Neck Disability Index is similarly suited for analysis of cervical spine products. Such regional outcomes measures should be coupled with a Visual Analog Scale for pain. A numerical score based upon symptoms and limitations in routine activities of daily living is compiled. Preoperative and postoperative time points are compared to determine if a subject improves as a result of treatment, and if the improvement is maintained over the course of the study period.

C. Revision or Reconstruction Prevalence

A revision is defined as a procedure that is performed on the replaced disc to remove and/or replace any component(s) that were implanted at the index operation. The prevalence of these occurrences should be calculated. In addition, any subsequent procedures related to the index level should be reported. This would include posterior fusion leaving the arthroplasty in place, decompression, facet rhizotomy, etc.

D. Radiographic Analysis

Measurements made on radiographs to determine implant position/migration should be defined and reported. There are not currently well-defined methods in the literature. The measurement techniques should be proposed by the sponsor. The sponsor should also propose the definition of a radiographic success and a “radiographic failure.”

Radiographic motion estimates from flexion and extension radiographs should be performed to demonstrate preservation of motion⁸

Radiographic evaluation of the adjacent segment degeneration should be reported.

Standardized benchmarks

Disagreement exists within the spine community over what precisely constitutes a “successful” back pain patient outcome. On the one hand, objective measures, such as those obtained from serial radiographs, can be used to assess changes of disc replacement components. On the other hand, subjective measures, such as questionnaires, indicate the patient’s own assessment of the performance of their disc replacement. Objective and subjective measures can produce contradicting depictions of disc replacement performance. Nonetheless, a combination of these two types of measures provides clinicians with the most comprehensive view of the success of the patient’s treatment.

Patient and study success

When quantitative values are applied to these variables, “success” can be determined per patient and for the study. Patient success is attained when a subject meets the quantities defined in all variables. The standardized quantities for the above variables are:

Major device related complication prevalence = 0

Improvement in standardized outcome measures of 20 to 30 percent (choice within this range will depend on the pre-operative score; the worse the score, the greater will be the expected improvement)

Revision prevalence = 0

Radiographic failure prevalence = 0

Neurologic complication rate = 0

A quality of life measure can be used as well as a further measure of outcome, but is not required. Study success is attained when at least 95% of subjects are deemed patient success OR equivalency to the control group is demonstrated with a 95% confidence interval. However, the final determination of a particular disc replacement’s safety and efficacy will require other considerations, including public health needs and the benefit (efficacy) to risk (safety) ratio. For example, a complication prevalence greater than 0 may not necessarily preclude a determination of safety and efficacy (i.e., market approval) if the disc replacement meets a public health need and specific outcome scores are sufficiently improved.

Number of subjects and data gathering intervals

Based on the above definition of “study success” (i.e., at least 95% of subjects deemed “patient success”), the sample size should be no less than 235, the number of subjects needed to detect a difference of 5% between the disc replacement study device and the “study success” definition, where an 8 point confidence interval is desired with a 95% confidence level. In a randomized prospective study design, the product must score no worse than an FDA approved control group.

Data for disc replacement clinical studies should be gathered (at a minimum) preoperatively, immediately postoperatively, and at 6 weeks, 6 months, 12 months and 24

months postoperatively. An endpoint prior to 24 months will be considered based upon justification from the sponsor. Data from 5-10 years followup are considered critical discriminators^{5,12} and provision should be made for their reporting (may be in pre- or post-approval period depending on initial safety and effectiveness data.)

Appendix I

Method of Defining Standardized Benchmarks

The development of standardized benchmarks was accomplished by consensus. The consensus was determined by a group of spine surgeons and biomechanics experts specializing in spine surgery and was kept to a small number to expedite the development of the guidelines. Medline searches were conducted on 9/16/04 using the terms “spinal disc arthroplasty,” “total disc arthroplasty,” “disc arthroplasty,” and “spinal disc replacement.” Additional searches were conducted on 10/7/04 using the terms “prosthetic disc nucleus,” “Acroflex,” “Aquarella,” “ProDisc,” “Charite disc,” and “Bryan disc.” Individuals on the working group supplied additional references and were reviewed and considered for inclusion. This group was assembled with the approval of the leadership and the members of the American Academy of Orthopaedic Surgeons, Cervical Spine Research Society, the North American Spine Society, and the Scoliosis Research Society. These organizations exist to advance knowledge of the spine in health and disease and to provide a forum to stimulate the exchange of knowledge concerning education, research, and treatment of disorders of the spine. The members of the team were:

Bill Christianson ⁺	OSMA
Bryan Cunningham M.Sc. ⁺	SRS
Brian Doherty, Ph.D.	CSRS
Lisa Ferrara, Ph.D.c	NASS
Jove Graham	FDA Liaison
Seth Greenwald D.Phil.	Orthopaedic Device Forum
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⁺Conflict of interest is disclosed. While every effort to minimize such conflicts among this group have been made, some members by virtue of their position and/or experience had inherent conflict of interest. Their input to the consensus process was important enough to warrant participation, and conflict of interest was managed with appropriate disclosures.

Appendix II

Literature search and level of evidence definitions can be added (if desired).

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