Guidance for Industry and FDA Staff

Clinical Data Presentations for Orthopedic Device Applications

Document issued on: December 2, 2004

For questions regarding this document contact Barbara Buch, M.D. at 240-276-3737 or by email at barbara.buch@fda.hhs.gov.

C·D·R·H
Center for Devices and Radiological Health

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

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

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

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/ode/guidance/1542.pdf, or to receive this document by fax, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number (**1542**) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Clinical Data Presentations for Orthopedic Device Applications

This guidance document 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 document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

1. Introduction

This guidance document is intended to provide you with recommended general clinical data presentation formats for premarket notifications (510(k)s), investigational device exemption (IDE) annual progress reports, premarket approval (PMA) applications, and annual and post-approval study reports for orthopedic implant devices. FDA is issuing this document to help ensure consistency and understanding between FDA and sponsors when discussing and presenting clinical data. We hope this guidance will conserve FDA and industry resources and facilitate timely review.

The data presentation formats described in this guidance document are intended to standardize presentations to facilitate review of Orthopedic Devices Branch (ORDB) submissions. The descriptions and definitions used in this document are commonly used in ORDB but may not be applicable to submissions in other product areas.

This guidance document is not intended to provide you with information regarding the presentation of preclinical data, nor is it intended to describe all elements required for 510(k)s, IDEs, or PMAs. This guidance document supplements other FDA publications on 510(k), IDE, and PMA submissions and should not be construed as a replacement for these documents.

Premarket Notification -510(k) Information

For general information on 510(k), refer to 21 CFR 807.87 and "How to Prepare a 510(k) Submission" in CDRH's Device Advice at http://www.fda.gov/cdrh/devadvice/314.html. In addition, there may be other guidance documents specific to your type of device located on the FDA website, http://www.fda.gov/cdrh/guidance.html.

Investigational Device Exemption Information

For general IDE information, refer to 21 CFR Part 812 or to the "Guidance on Investigational

Device Exemptions Policies and Procedures," available at http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

Investigational Device Exemption Report Information

There are additional elements that are necessary for the completion of an IDE report and they are outlined in FDA's document titled, "Suggested Format for IDE Progress Report," available at http://www.fda.gov/cdrh/devadvice/ide/reports.shtml.

Premarket Approval Application (PMA) Information

For general PMA information, refer to 21 CFR 814 or http://www.fda.gov/cdrh/devadvice/pma/app_methods.html. In addition, there may be other guidance documents specific to your type of device located on the FDA website, http://www.fda.gov/cdrh/guidance.html.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents 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 should be addressed before your device can be marketed. 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 follow 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 http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. General Data Presentation: Recommended Elements

For all data presentations, we recommend that you clearly identify the number of patients evaluated at a given timepoint in any data presentation, in addition to the rate of improvement, for example, "64/75 patients at 3 months" rather than "85% at the 3 month timepoint." For any table, a clear description of the population on which it is based is important. In other words, if the result is 64/75, but the population was 100 patients, you should account for the remaining 25 patients.

We recommend that you consider the examples of formats for data presentation in this document when you are designing your study to better assure that you collect adequate data. We recommend that you provide the information below, as appropriate to support a 510(k), IDE annual report, or PMA (including PMA annual and post approval study reports):

Description of the patient population

This description includes a detailed discussion of the patient demographics in each treatment group (see also section 3. **Description of Study Population**). We recommend that you include any important demographic factors that may influence outcomes. This may include, but is not limited to:

- age
- gender
- co-morbid conditions
- work status
- smoking history
- diagnostic groups.

Time course distribution of patient accounting

This includes an accounting of the status of each patient at each follow-up interval (e.g., theoretical follow-up, deaths, reoperations, revisions, removals, supplemental fixations, expected follow-up, actual follow-up, and follow-up rate). These are discussed in section **4.**

Patient Accounting. We recommend that you include a clear description of the evaluation intervals pre- and post-treatment. We recommend that an appropriate follow-up window for the evaluation interval be pre-defined in the IDE protocol. We recommend the windows around the intervals be distinct, as small as possible, and not continuous, for example:

- 6 weeks ± 2 weeks
- 3 months ± 2 weeks
- 6 months ± 1 month
- 12 months ± 2 months
- 24 months ± 2 months
- annually ± 2 months.

FDA believes that defining evaluation windows before initiating the study is optimal for comparing homogenous patients at each different follow-up timepoint in the postoperative period.

Written (narrative) descriptions of adverse events

Written (narrative) descriptions of adverse events should include both details of the events and demographic information (see Section 5. **Safety**).

The details of the events should include:

- any subsequent surgical interventions
- deaths
- protocol deviations
- severe complications that occur, including any actions taken as a result

- resolutions.

The demographic information should include:

- device implanted
- diagnosis
- level or site of implantation
- pertinent medical information.

We also recommend that you include any other information related to any association between the device and the event described.

After identifying these events, if you change your study protocol or surgical technique, we recommend that you describe the changes and explain how these changes avoid or reduce the occurrence of adverse events.

Time course distributions of all adverse events for all patients receiving a treatment or implant

We recommend that you present this distribution in a table (see Tables 3 and 4). A separate table should be presented to describe any subsequent surgical interventions (see Table 5).

Time course distributions of effectiveness parameters

This distribution includes the following parameters:

- pain
- function
- radiographic assessment of fusion
- radiographic assessment of the implant
- health related quality of life
- return to work status
- other evaluation parameters appropriate to your endpoints.

These time course distributions should provide the number of patients who meet each success criterion for each parameter (e.g., as for pain, function) and should provide the number of patients evaluated within a given group for each parameter (see Table 6).

Time course distributions of the individual patient success rates

This distribution should include success rates for all patients over the course of the study (see section 7. **Patient Success Results** and Table 7). This allows for an appraisal of the patients' progress over time.

For each of the data presentations above, we recommend that you stratify patients into the following subgroups, as appropriate for the particular study design:

- investigational and control groups
- group being studied (e.g., bilateral joints, unilateral joints, single level fusion, two level fusion, non inflammatory, inflammatory arthritis)
- separate subgroups, where appropriate, unless the study is masked
- separate presentations for patients implanted outside of the study (e.g., compassionate use or continued access patients).

We also recommend that you provide separate presentations for patients who do not follow the study protocol. These patients may include those who did not meet all of the inclusion or exclusion criteria, did not receive all of the study implant components, or patients who are evaluated outside of the protocol-established time windows. Therefore, we recommend that you provide clinical and statistical rationales for their inclusion and for pooling of these patients' data.

General Safety Event Reporting

We recommend that you report all adverse events, regardless of rate of occurrence, as they occur throughout the study.

We may recommend additional or more detailed data presentations for your application if describing specific subsets of clinical data or other information will further elucidate the clinical performance of your device.

3. Description of Study Population

We recommend that you provide a complete description of the patient population. This verifies that the groups being evaluated are similar and that the variances in the study groups are similar enough to compare the groups statistically and clinically. We recommend that you list the demographics and all of the diagnoses and subgroups involved in the investigation, indicating the number of patients that have that diagnosis. This list should incorporate any important patient characteristics that may influence patient outcomes, such as preoperative work status, education, and smoking status. Depending on the inclusion and exclusion criteria, we recommend that you also include confounding factors such as the number of patients who abuse alcohol, are involved in worker's compensation or medical litigation, race (if appropriate), medical co-morbidity, previous surgery, degree of medication use, and involvement of other adjacent or nonadjacent joints or spinal levels. We also recommend that you include treatment demographics, such as operative times, blood loss, length of hospital stay, and post operative bracing, for each treatment group. Table 1 is a sample table for presenting demographic information described above.

Table 1 Demographic Information

		I	C
Number of patients			
Men/women			
Mean age, year (range)			
Education level	<High School		
	High School Diploma		
	>High School.		
Smoking	Yes		
	No		
Alcohol use	Yes		
	No		
Preop Employment Status	Working		
	Not working		
Medical Conditions	Diabetes		
	Cardiac, etc		
Diagnosis (# of patients and # of joints)	Osteoarthritis		
	Osteonecrosis		
	Rheumatoid arthritis		
	Other		

I= investigational group; C = control group

4. Patient Accounting

Table 2 below is a sample table for patient accounting. Refer to section **8. Elements of Clinical Data Presentations** for complete definitions of each of the elements included in that table.

Table 2 Patient Accounting

	Preop		6 wks		3 mo		6 mo		12 mo		24 mo		36 mo	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Theoretical														
Deaths (cumulative)														
Failures (cumulative)														
Expected														
Actual[A]														
Actual[B]														
% Follow-up														

I = investigational group; C = control group

[A]Patients with complete data for each endpoint, evaluated per protocol, in the window time frame.

[B]Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting).

Where appropriate, an additional line for patients not yet overdue (see **8. Elements of Clinical Data Presentations**) may be added to this table.

As stated in section **8. Elements of Clinical Data Presentations**, "Actual" includes those patients with complete assessment evaluations collected for each endpoint as per the protocol. However, we understand that not all studies operate under ideal conditions and, in some circumstances, not all patients are followed up at the intended time intervals or circumstances prevent collection of all data points to determine patient outcomes. Therefore, it may be appropriate to provide a patient accounting table that also includes any patient who has been followed during the study regardless of whether data for all study end points has been collected. This is referred to as "all evaluated" accounting.

For an IDE or PMA report or an original PMA, FDA recommends a minimum of 85% follow-up of patients in each study cohort to maintain the power of the study, avoid the potential for bias, and provide sufficient data for analysis. If an IDE or PMA report does not show that the study is meeting this goal, we recommend that you provide an adequate explanation for not meeting this goal and describe what steps are being taken to achieve adequate patient follow-up.

FDA may recommend that you perform a sensitivity analysis at the time of final data submission to assist in explaining, both clinically and statistically, the pooling of those patients with incomplete outcome data or out of window data with those patients who have complete data collected per the protocol. Your analysis should clearly define the number of patients evaluated within the time windows, before the time window, or after the time window for each evaluation interval.

5. Safety

We recommend that you organize the safety outcomes into two general categories: adverse events and subsequent secondary surgical interventions.

Adverse Events

We recommend that you record and report all preoperative, operative, and postoperative complications, whether device-related or not. These include anticipated and unanticipated complications. Pain, neurological, and function symptoms are categorized as complications when a patient's complaint for any of these symptoms results in an unscheduled visit or when a patient presents with new or worsening symptoms as compared to the previous visit. We recommend that you categorize or group adverse events according to the World Health Organization recommendations[1] or another accepted method of categorizing adverse events. We recommend that you make a determination of device-related, operative site-related, and systemic (non-device related) events, if possible.

[1]World Health Organization (WHO), International Classification Systems, http://www.who.int/classifications. See also Chapter 5, Mental and Behavioural Disorders in **The International Statistical Classification of Diseases**. WHO. See also the Primary Care Version and Educational Kit in Related Health Problems, in **International Classification of Impairments, Disability and Handicaps**. WHO.

Table 3 below illustrates one way of presenting adverse events for a total joint device, stratified by operative site and systemic events. The time course of adverse events follows the same logic as the patient accounting table. Each adverse event is identified by listing it vertically down the left column of the table. Across the top row of the table are the scheduled follow-up visits. The table should include the number of occurrences for each type of event and the number of patients evaluated at each time interval.

Table 3 Adverse Events (Sample for Total Joint Device)

	Immed. Post-op		**3 mo**		**6 mo**		**12 mo**		**24 mo**		**36 mo**	
	I	C	I	C	I	C	I	C	I	C	I	C
	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=
Operative Site Events												
Infection												
Wound dehiscence												
Dislocation												
Fracture implant liner, head etc.												
Fracture bone												
Other												
Systemic Events												
Myocardial infarction												
Pulmonary emboli												
Urinary tract infection												
Other												

N = number of patients evaluated at that time period.
I = Investigational group; C = Control group

Note: If patients experience more than one adverse event, we recommend that the narratives describe recurrent events.

Table 4 below is another similar format for presenting a time course distribution of adverse event for a spinal implant system.

Table 4 – Adverse Events (Sample for Spinal System)

	Op		D/C-6wks		6wks-3mo		3-6 mo		6-12 mo		12-22 mo		22-26 mo		26-34 mo	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=	N=
Implant Related																
Implant displacement /loosening																
Malpositioned implant																
Non-union																
Subsidence																
Infection																
Surgery Related																
Anatomic/ technical difficulty																
Dural injury																
Retrograde ejaculation																
Back/leg pain																
Graft site																
Neurological																
Spinal event																
Vascular, intraoperative																
Vertebral fracture																
Systemic																
Urinary tract infection																
Cardiac events																
Etc.																

I = Investigational group; C = Control group

N = number of patients evaluated at that time period.

Note: If patients experience more than one adverse event, we recommend that the narratives describe recurrent events.

Subsequent Secondary Surgical Interventions

Some adverse events lead to a subsequent secondary surgical intervention. We recommend that you report subsequent secondary surgical interventions, separately from the presentation of other adverse events. The reporting of these events is performed in the same manner as deaths. For example, a patient was revised at or prior to the immediate post-op examination. We suggest that you report this revision under the immediate post-op follow-up visit. If, at some time between their immediate post-op examinations and their individually scheduled 3-month follow-ups, 2 additional patients had revisions, then you should report these 2 revisions at the 3-month follow-up timepoint because the examinations took place between the immediate post-op examination and the 3-month follow-up.

FDA categorizes subsequent surgical interventions as follows:

- revisions
- removals
- reoperations
- supplemental fixations
- other interventions.

Refer to Section **8. Elements of Clinical Data Presentations** for complete definitions of each of above categories of subsequent surgical interventions.

We recommend that you incorporate the definitions for subsequent secondary surgical interventions listed above into an IDE protocol, to assure consistency in reporting outcomes.

We recommend that you capture the reason for each subsequent secondary surgical intervention and the action taken (e.g., replacement of a screw, placement of extra bone grafting material, revision of a hip stem). Along with the presentation of the subsequent secondary surgical interventions pooled into the five categories above, we recommend that each category be further stratified. For example, the revision category may be stratified into separate categories such as "revision for translated cage," "removal of screws," depending on the reasons identified in a particular study. As another example, the "removal" category may be stratified into removal for pain at the operative site after fusion or pseudoarthrosis, etc.

FDA believes that some reasons for performing a removal may constitute a failure; however, this is also dependent on the device type. We recommend that you clearly identify which reasons for removal constitute a patient failure and provide a rationale. For example, removal of a cage at any time should constitute a failure, however, removal of a pedicle screw system after fusion may not. If removal surgery is recommended in the protocol for a given implant, we recommend that you clearly indicate in your IDE protocol how such removals will be interpreted in terms of success and failure of the study. Additionally, we recommend that you identify any other subsequent surgical intervention that constitutes a patient failure.

Table 5 below illustrates one way of presenting subsequent surgical interventions. You should indicate the number of patients who underwent the specific intervention at each timepoint. If the

number of implants differs from the number of patients, we recommend that you provide explanatory descriptions in the adverse event narratives.

Table 5 Subsequent Secondary Surgical Interventions

Type	Op		D/C		6 wk		3 mo		6 mo		12 mo		24 mo		Total events		# patients	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Revisions																		
Removals																		
Supplemental Fixations																		
Reoperations																		
Other[A]																		
Total																		

I = investigational group; C = control group

[A]The "other" types of surgical interventions should be defined.

Any events occurring after 24 months may be placed in an additional column headed "more than 24 months."

6. Effectiveness

The effectiveness clinical summary submitted in support of a PMA should be more detailed than that of an annual report.

When an evaluation method such as a Harris Hip Score is used, we recommend that patient results be presented as the number of implants with each rating score.

We recommend that you summarize your results in tabular form and include each stratified group being studied (e.g., bilateral joints, unilateral joints, single level fusion, two level fusions, non inflammatory arthritis, inflammatory arthritis). We recommend that you provide a separate table for patients implanted outside of the study (e.g., compassionate use or continued access patients). See the example in Table 6.

Table 6 presents a typical orthopedic clinical evaluation system (Harris Hip Score). The number of patients and procedures that meet each rating is listed under the Total Score, Pain Score, and Function sections. Similar tables can be used for other endpoint assessments.