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Advisory Panel Meeting:

ORTHOPEDICS AND

REHABILITATIVE DEVICES

OPEN SESSION

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P R O C E E D I N G S

(11:50 a.m.)

**Agenda Item: Call to Order, Opening Remarks,
Conflict of Interest Statements.**

MR. DEMIAN: Good morning, everyone. We are ready to begin this meeting of the Orthopedic and Rehabilitation Devices Panel.

My name is Hany Demian and I am the executive secretary of this panel. I would like to remind everyone that you are reminded to sign in on the attendance sheets which are available at the tables by the door.

You may also pick up an agenda and information about today's meeting, including how to find out about future meeting dates through the advisory panel phone line and how to obtain meeting minutes or transcripts.

I will now read the statement that is required to be read into the record, and this is the conflict of interest statement.

This is for October 8, 1998, conflict of interest statement. The following statement announcement addresses the conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of any impropriety.

To determine if any conflict exists, the agency reviewed the submitted agenda, all financial interests reported by the committee participants.

The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employees' financial interest.

However, the agency has determined that participation by certain members and consultants, the need for whose services outweigh the potential conflicts of interest involved, is in the best interests of the government.

Waivers have been granted for Drs. Cato Laurencin, David Hackney, Edward Hanley, Kinley Larntz, David Nelson, Harry Skinner, because of their interests in firms that could potentially be affected by the panel's decision.

A waiver is currently on file for Dr. Albert Aboulafia as well.

The waivers permit these individuals to participate in all matters before the panel during today's discussion.

Copies of these waivers may be obtained from the agency's freedom of information office, room 12-A-15, of the Parklawn Building.

We would also like to note for the record that the agency took into consideration other matters regarding Dr. Aboulafia, Dr. Edward Hanley, Barbara Boyan, Daniel Clauw, Thomas Ducker, and Michael Yaszemski.

Each reported involvement with firms at issue, but

on other matters, unrelated to the meeting's agenda. The agency has determined, therefore, that they may participate fully in today's deliberations.

In the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interests of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Before turning this meeting over to Dr. Boyan, I would like to introduce our distinguished panel members, who are generously giving their time to help the FDA in matters being discussed today, and other FDA staff seated around this table.

We will just go around the room and have everybody introduce themselves, and give their area of expertise and where they are located at.

DR. BOYAN: I am Dr. Barbara Boyan. I am a professor and director of orthopedic research at the University of Texas Health Sciences Center at San Antonio. I am a cell biologist, particularly interested in bone and

cartilage cell biology.

DR. CHENG: My name is Edward Cheng. I am from the University of Minnesota. I am an orthopedic surgeon with an interest in orthopedic oncology and adult reconstruction.

DR. SKINNER: My name is Harry Skinner. I am professor and chair of orthopedic surgery at the University of California, Irvine, and professor of mechanical and aerospace engineering at UC Irvine. My specialty is joint replacement surgery.

DR. YASZEMSKI: I am Michael Yaszemski. I am an associate professor of orthopedic surgery and bioengineering at Mayo Clinic, Rochester, Minnesota.

My clinical interest is spinal surgery. My research interest is statistical engineering for bone replacement.

DR. BOYAN: While you are introducing yourselves, some of the audience is actually sitting outside watching us on video, and they are having difficulty hearing us, the ones that aren't in the room. You have to speak very carefully right into the microphone.

DR. LAURENCIN: I am Dr. Cato Laurencin. I am a clinical associate professor at MCP Harmon Medical School, and also professor of chemical engineering at Drexler University.

DR. ABOULAFIA: My name is Albert Aboulafia. I am an orthopedic surgeon at Emory University School of Medicine in Atlanta, Georgia. My area of interest and expertise is orthopedic oncology.

DR. WITTEN: I am Celia Witten, division director of DGRD.

MS. MAHER: I am Sally Maher, director of regulatory affairs for Johnson and Johnson, Professional, and I am the industry representative.

DR. HOLEMAN: Doris Holeman, chair of the department of nursing, Albany State University in Albany, Georgia.

DR. DUCKER: Tom Ducker. I am a neurosurgeon, in practice in Annapolis, and a professor at Johns Hopkins.

DR. NELSON: David Nelson. I am an orthopedic hand surgeon in San Francisco.

DR. LARNTZ: Kinley Larntz. I am a statistician. I am professor emeritus of statistics at the University of Minnesota.

DR. NAIDU: Sanjiv Naidu, hand surgeon at the Hershey Medical Center, Penn State, in Hershey, Pennsylvania.

DR. HANLEY: Ed Hanley. I am an orthopedic surgeon from Charlotte, North Carolina. My special interest is in spine.

DR. HACKNEY: David Hackney. I am a professor of radiology at the University of Pennsylvania. I am a neuroradiologist with an interest in brain tumors and spine imaging.

DR. CLAUW: Dan Clauw. I am an associate professor of medicine at Georgetown University Medical Center, and chief of the division of rheumatology. My research interest is chronic pain.

MR. DEMIAN: Thank you. At this time I would like to turn the meeting over to our chairperson, Dr. Barbara Boyan.

DR. BOYAN: Good morning. My name is Dr. Barbara Boyan. I am the chairperson for this meeting.

Today the panel will be making recommendations to the Food and Drug Administration on a preliminary background document pertaining to the development of investigational device exemptions, applications for spinal device assemblies.

I would like to note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

First, we will have Thomas Shope, from the Office of Science and Technology, give a presentation on the Y-2-K problem. Dr. Shope?

Agenda Item: Preliminary Background Document for

**the Development of Investigation Device Exemption (IDE)
Application for Spinal Assemblies. FDA Presentation.**

DR. SHOPE: Good morning. You are guinea pigs today for the first of a series of presentations we plan to do with each of the advisory panels to try to benefit from your expertise, and also to help raise a little bit of awareness with regard to the potential problems stemming from what is known as the year 2000 date problem.

I would encourage you, if you have some feedback on the level of this presentation, its usefulness or whether it is at about the right level and about the right link for a panel coming to this fresh, to share those with either the executive secretary or myself, because we would like to improve this if we can.

The year 2000 problem has been described a lot of different ways. Some of the things that you see in the literature, doomsday is talked about a lot.

It certainly can be a medical device problem for those medical devices that employ computers and have been programmed to use just two digits to represent the year where that is a problem.

It is certainly an issue in health care, as much of the health care operations these days are dependent on computers, computer information systems, data bases, all kinds of computerization these days.

It is a significant issue in every health care organization to make sure that their systems are appropriately evaluated, mitigation done where necessary, and everyone is prepared for the new millennium.

The medical director at the Department of Veterans Affairs coined the millennium bug system to describe this. I just put that up to make my slide balance.

This is something that sort of got me thinking about this when I read an ad, actually, a couple of years ago that said about 80 percent of the existing PCs are unreliable when faced with this year 2000 date and their internal clock mechanisms.

Clearly, many PCs are used as parts of, or to control medical devices. I have listed some examples here on this slide, systems that control pace makers or pace maker programming, interrogation, many monitoring type systems that use a PC to collect data centrally from remote locations, many clinical lab instruments these days communicate with computer systems, just an example of the kinds of products that use PCs.

Another quote from a couple of years ago from some of the literature was the largest computer initiative in history needs to begin today, for those that hadn't started getting ready for the year 2000. That was trying to raise some awareness.

Another ad, this one from a company that was to help the hospitals consult on the problem, is that 25,000 health care systems will not be working properly.

I don't think this reflects medical devices necessarily, but more the information systems in health care facilities.

It is clear that there are products that can have problems. Microprocessors or PC controlled products, just plain stand alone software applications, I think a good example of this is radiation treatment planning systems, that might be planning treatment for brachiotherapy or teletherapy and can't do the source strength calculation well because the years get confused.

There are lots of device interfaces to data bases, to record keeping systems, where data information may be passed back and forth.

There are all kinds of products like you microwave at home that display the dates and the time. Whether it is part of the actual functioning of the device is not always clear.

There are certainly many products with date and time sensitive developments.

So, what is this problem that we are talking about? I think by now most people have heard about this problem.

It is the failure of a system to process properly or display dates due to the date being represented using only two digits for the year. So, a little confusion arises with 00 or 01. Is it 1901 or 2001.

If that information is used in a calculation or an algorithm, it can lead to incorrect results.

We did a definition of compliance when this problem doesn't exist, in a letter that we sent out in January.

This definition is based on the federal acquisition regs about year 2000 compliant products. It basically means the product is impervious to the change in the date. Nothing unusual happens, and no problems are encountered. It works before and after the turn of the clock on December 31, 1999.

The requests that we are coming to the panel with here are sort of three fold. One is to seek your advice on particular products in your domain of expertise where this might have been a problem.

We have been thinking about this here at the center for a while. We have been communicating a lot with the manufacturers. I think there is always a chance to overlook some issues.

So, we are interested in hearing from you if there are products that you are familiar with that might be

subject to this kind of a problem.

Identifying those products that could present a risk to patients if they are not addressed is our primary concern.

There are a lot of date problems that really don't present a risk to patients. I think part of the job the health care facilities have is sorting out the difference between the ones that are just going to be a little bit of a bother versus the ones that can present a risk.

We are also open to suggestions from you as to any other actions that the center ought to be taking, or that FDA ought to be taking, to deal with this problem in terms of information clinicians need, information patients or consumers needs, information we should be giving to the industry about actions they need to be taking.

It is just meant to be an awareness raising brief discussion here.

I will mention that most of the information relevant to this issue for the Center for Devices and Rehab Health can be found on our web site.

There we have established a data base where manufacturers who have products where they have identified a problem can list those products and talk about the kinds of solutions they are going to offer for those problems, as well as a lot of the letters and guidance documents that we

have put out.

I am not going to get into real details, but just mention that that is there.

Some of the things we have done so far in the center are letters to manufacturers asking them to share information on their products, all past production that could be impacted by this problem, and we are establishing this data base.

We have provided a guidance document to manufacturers. That was one of your handouts published in the Federal Register back in June that tells manufacturers what we expect of them. The data bases I mentioned.

We are continuing to monitor and assess. As we hear about products that might potentially have a problem, we want to make sure we follow up on any that need attention in terms of potential patient risk.

We see in the future, between now and the year 2000, the need for some educational activities to prepare clinicians and the public for dealing with questions that come up in this area.

I would encourage you, if you have concerns, suggestions or products that we ought to be especially concerned about, to communicate either with the executive secretary here for this panel or directly with me as sort of the stuckee on the year 2000 thing around here. That is my

address.

There is some more information on the slides that were handed out that go into a little bit more detail on some of our activities. I am not going to take time here, but I want to just share some of that with you, some of the characteristics of our data base and some of the other things that we have been doing.

With that, I will conclude. If you want to have a discussion, I don't know what your plans are here. I will certainly be around for a few minutes, if there are particular issues that the panel might like to raise in just a minute or so.

DR. BOYAN: Thank you very much. I think in the interests of time, because we did go a little bit over earlier today, that what I would like to have the panel do, all of us, I am sure, thinking about this a lot in our own workplace, and if you have information that you would like to bring to the FDA's attention, to either share it with Mr. Demian or Dr. Shope, make a note on one of the pieces of paper by your place, or contact them by e mail or phone after the panel meeting.

We are now going to proceed with the discussion of the preliminary background document, which involves ideas pertaining to the development of investigational device exemptions, applications, for spinal assemblies.

I would like to ask Dr. Orlee Panitch, medical officer for the Office of General and Restorative Devices, to provide the FDA presentation.

DR. PANITCH: Again, I am Orlee Panitch. Good morning, and thank you for coming. The panel has seen a lot of spinal products and we are looking forward to bringing some closure to some of the questions that we have had.

The who, what, when, why, where and how of guidance documents. Before I start this, I just want to reiterate that what we are discussing today is a background document and is not a draft guidance at this point, and that will come up again.

Regarding the who, who is involved in the process and the development of this guidance document. Really, everyone in this room is.

Anyone who has anything of any relevance to say, and that will include, at the very least, the panel, the practicing community, industry, academics and, of course, the government.

Again, now what is the guidance document. The idea of a guidance document is to provide a set of ideas and recommendations to, again, the practicing community, manufacturers and the FDA so that IDEs which are presented have some consistency to them.

Why? Why we need a guidance document is to help,

one, the reviewers in the FDA, to help manufacturers, the practicing community, to all improve the quality of health care.

It is to help ensure consistency. It is to help facilitate the high work load that is presented to the FDA, so that we can provide timely reviews. It is to help manufacturers design preclinical and clinical testing in the least burdensome way.

The when of this is when will this become a true guidance document. That is going to involve a discussion of the process.

The process of developing this document has begun several months ago in the development of this draft background guidance.

From here we will be discussing it today and over the next several months. The FDA will put together these comments and prepare a draft guidance.

That guidance will then need to go through the GGP process, which is good guidances, which is a new formalized process that will include notice and comments.

This brings us to the where. Where will this be found. Eventually, notice of this document will be available through the Federal Register and through the GG process on the internet.

Now, as far as the how, by now everyone has gotten

a copy of, or has hopefully had a chance to peruse the document.

What we plan to do today is to highlight the major points that we would like some additional feedback. We invite comments from the panel, from the practicing community and industry, to provide any further comment on other portions.

Because this is a significant guidance which involves many manufacturers and a large part of the FDA work load, what we will do is discuss this and, again, take this through the whole GGP process.

The next two slides, what I have provided here is what is in the contents of the background document.

There are 10 elements that are put forth by a sponsor in describing an IDE. These are the first five and these are the next five.

What we hope to do is concentrate today on the investigational plan. There are nine questions that we have posed to the panel, and the next nine slides are bullet points of the relevant points. I am going to read a little description of what our problems are and how we would like the answers and comments addressed.

Question one. Spinal clinical assessments of pain, function and neurological status are performed pre and post-operatively.

FDA has recommended a number of the instruments to assess pain, function and neurological status in this document.

Please comment upon their use. For example, minimal scores for entering into study, success criteria, and what should be considered primary or secondary assessments.

Please comment on any other instruments that may be used to assess pain function in neurological status, and please consider lumbar and cervical levels independently.

I am going to go through all the questions and we will come back to them individually later.

Number two deals with radiological assessments, which are used to evaluate spinal assemblies intended for fusion and non-fusion.

Radiographic assessments of spine can include all the listed elements.

We believe that sponsors should take into account the specifics of their spinal assembly design when choosing a radiographic assessment tool; for example, the shape, rigidity, implantation site and features which may obscure visualization.

Please comment on the types and methods of radiographic methods necessary to define successful fusion.

We have an additional question regarding CT. CT

is frequently recommended for visualization of a fusion mass around or inside spinal assemblies.

Please comment upon the use of CT or other radiographic assessments for this purpose. Is it appropriate? What techniques should be used, and what would constitute validation of the proposed approach.

Question three is a short one. Please comment upon the specific types of information that would be required to modify the current study duration of two years.

Please address the lumbar and cervical levels independently.

Question number four. Many spinal assemblies recreate or restore disc or vertebral body height in the spine, for example intervertebral body fusion devices and disc or nucleus replacement devices.

How should long-term restoration of height be used in determining the safety and effectiveness of the spinal assembly.

Should these be primary or secondary end points. Please comment upon how this information should be collected; for example, the appropriate time to measure baseline values and methods for measuring each.

Question number five. For spinal assemblies not intended to fuse motion segments, such as a disc replacement device or nucleus replacement device.

Please comment upon what criteria should be used to select patients for such surgery, and how clinical and radiographic success should be determined.

Additionally, please comment upon what would be an appropriate control population when designing a clinical study.

Question number six. Patients with tumors metastatic to the spine have, using conventional treatments, a limited life expectancy.

Additionally, these patients may be severely ill with other manifestations of their cancer and, therefore, may not respond to spinal surgery, similarly, as compared to non-terminally ill patients.

Consequently, the evaluation of these patients should take into account the extent and severity of their illnesses.

FDA needs to interpret the clinical outcome of these patients, despite the diversity of illness and outcome in this patient cohort as a whole.

Please comment upon what would be appropriate parameters and success criteria for determining the safety and effectiveness of a spinal assembly intended for this patient population.

Prior orthopedic and rehabilitation device panels have recommended assessing health related quality of life as

measured by the SF36 or the SF12.

Please comment upon what information is captured by these assessments and how this information should be used in determining the safety and effectiveness of a spinal implant.

Regarding patient satisfaction, again, prior orthopedic panels have recommended including this assessment.

Please comment upon how this information should be used when determining the safety and effectiveness of a spinal assembly.

Additionally, please comment upon how this information should be collected.

Finally, question number nine has multiple parts to it. As part of the study protocol, sponsors should provide information regarding the subsequent surgical interventions that may occur during the study.

These procedures are typically stratified among removals, revisions, re-operations and supplemental fixations.

However, it is often difficult to discern which of these subsequent surgical interventions should be considered a patient or a study failure, and which is an unanticipated or anticipated adverse event, either secondary to the type of device implanted or secondary to progressive disease.

For many reasons, such as the discretion of the surgeon, patient request or component failure or loosening, a subsequent surgical intervention is performed.

For each of the subsequent surgical interventions of removal, revision and re-operation, please describe how to interpret the types and occurrence rates when determining the safety and effectiveness of a spinal assembly.

Please consider the following when formulating your response: reasons that would constitute patient or study failure and specific types of assemblies that are involved. That concludes the presentation.

Now I would like to go back to the individual questions.

DR. BOYAN: Thank you very much. I need just two minutes here to discuss something with Mr. Demian.

Okay, what I think we will do, so we can stay on track with the program, is break now for lunch until 1:15. Then we will come back and have presentations from the public as well as from professional societies, before we start taking up these individual questions.

We are now on break and we have 60 minutes, no more, no less.

[Whereupon, at 12:20 p.m., the meeting was recessed, to reconvene at 1:20 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:20 p.m.)

DR. BOYAN: Okay, we have permission from Mr. Demian to start without him. I have a couple of business items.

First, to remind all the panel members to speak directly into the microphone. For anybody from the audience that might speak, you need to be sure that you identify yourselves. I will remind you of this several times, to nobody forgets, every time you speak.

Now we are going to start the open public session of this meeting. I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone, as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing of the meeting disclose whether they have financial interests in any medical device company before making your presentation to the panel.

In addition to stating your name and affiliation, please state the nature of your financial interests, if any.

We have one request. I would like Dr. Thomas Zdeblick, a professor at the division of orthopedic surgery at the University of Wisconsin, to provide his comments on the preliminary background document for IDEs for spinal

assemblies. Dr. Zdeblick?

Agenda Item: Open Public Session.

DR. ZDEBLICK: Good afternoon. My name is Thomas Zdeblick and I thank you for this opportunity to present my views.

I am a professor of orthopedic surgery at the University of Wisconsin and a full-time spinal surgeon. I am also a spinal researcher, inventor and principal investigator of several FDA IDE studies.

In addition, I have experience in performing prospective randomized studies on two different occasions, one involving pedicle screw fusion surgery, and the other involving laparoscopic interbody cage fusions.

I would also state that I am a paid consultant with a spinal implant company. I have a research lab that is partially funded by grants from spinal implant companies, and I am a designer of spinal implants and currently receive royalties for those designs.

I would like to begin my comments by first congratulating the FDA on their intent to provide a more cohesive set of ground rules for performing spinal implant IDEs.

It has been frustrating to me over the last 10 years, as each new spinal IDE that I have participated in has been performed under a different set of ground rules.

That makes it difficult for me as a principal investigator, for my office in terms of the different follow up requirements, and for patients in terms of what is required of them.

For instance, it is clear to me that a prospective, randomized trial is not a viable method of evaluating spinal implants.

Early in my career I was able to do this on a select group of patients primarily because of the limited treatment options available at that time.

Patients now, partly due to the internet, are much more sophisticated. They know what is available in the marketplace. They will insist on the newest implant being placed, and they are often referred specifically for that implant.

It is not viable for those patients to be randomized to a control group which might entail the placement of an older device or no device at all. Many of those patients will simply refuse to participate in a study.

The evaluation of a spinal fusion is another topic with which the FDA has wrestled for many years.

Clearly, the gold standard for spinal fusion is histology. When I can obtain a fine section microradiograph such as this one, which shows solid trabecular bone growing from one vertebra to another through a spinal fusion

device, and biomechanically this also correlates with no motion, I can guarantee this is a solid fusion.

Unfortunately, this type of histology is not available to those of us performing clinical trials. What comes closest to this gold standard is the reconstructive CT scan.

This scan, when performed properly, can eliminate much of the metal artifact and can tell us whether a fusion is solid.

While this plane radiograph shows excellent position of an implant, it is difficult to assess its fusion.

However, on fine section CT reconstructions, you can see trabecular bone through the implant and hypertrophy both above and below the implant as evidence of a solid fusion.

I think if you look back at the histology I showed and then look at this section, you can be very confident that this is a very good way of assessing fusion.

If the FDA is looking for a gold standard for spinal fusion, it will not be found in plane radiographs or flexion extension films, but will be best found in fine section CT scans that can be independently reviewed by radiologists.

It is also clear that this type of solid fusion

occurs much sooner than the one-year time period. For example, this scan is from a patient at six months.

Most fusions occur between three and six months. If a fusion has occurred at that point, two-year follow up is superfluous.

This is even more clear in the cervical spine, where a follow up at six months may be more appropriate.

Also, it is clear that the two-year traditional follow up has not been supported amongst our professional societies and in our professional journals.

I am an editor for the Journal of Spine and on the program committee for the North American Spine Society and the Cervical Spine Research Society.

Articles submitted to those groups for publication or presentation often are done with a minimum of one year of follow up.

I would strongly encourage this body to adopt a more reasonable one-year follow up rule, rather than the tradition-based two-year follow up rule.

Finally, I wish to make one strong statement regarding subjective versus objective follow up criteria. When spinal implants are being evaluated by the FDA, they should be evaluated for their safety and effectiveness in performing the role in which they are intended.

In most instances this would mean spinal fusion.

Spinal fusion should be the end point and it should be the most important evaluation end point that the FDA utilizes.

Clinical evaluation and a particular pain relief should not be a major portion of this evaluation. Pain is a subjective response. Despite the sophistication of our current outcomes testing, it remains an elusive end point at best.

For the FDA to specify the amount of pain relief that must be obtained following an operation may over-step the bounds of the FDA.

The FDA should not be evaluating whether spinal fusion surgery in general is a successful operation. Rather, it should be evaluating devices whose goal is to obtain a spinal fusion.

In particular, the suggestion in this document that a minimum level of pain must be present before a surgeon performs a spinal fusion is, I feel, impinging upon our free practice of medicine.

Following pain is important and, if it should be followed, it should be followed in a reasonable manner. Specifically, a 15 point decrease in the osteoestria pain score, I feel, is unrealistic.

First of all, the 15 point decrease was chosen apparently because it is the mean improvement seen in several clinical studies. Choosing a mean as your

definition of success will guarantee a 40 to 50 percent failure rate.

Secondly, a 15-point decrease does not take into account the starting point of the patient's pain. In my opinion, if the FDA chooses to define pain as a success criteria, a 10 or 15 percent decrease would be more reasonable.

To reiterate, I would strongly encourage this group to minimize its reliance on pain outcomes in evaluating implants.

The safety and efficacy of a spinal implant is not dependent upon its amount of pain relief. Can you imagine evaluating the success of cardiac stent implants by the patient's sense of well being? No, they are evaluated by the patency of the coronary artery.

Similarly, spinal implant devices should be evaluated by their function; that is, obtaining stability or a solid fusion, and not upon subjective measures such as pain relief.

Thank you so much for giving me the opportunity to present my views. I would be happy to participate in further discussions or to answer any questions. Thank you.

DR. BOYAN: Thank you very much. Before I open the discussion to the audience making any comments, I would like to turn the microphone over to Mr. Demian, who is going to

read into the record -- when one of them is physically amongst us.

I would like to invite Dr. Scott Kitchel to the podium to make his comments, please. I remind you to state your affiliation with any companies and the nature of that affiliation.

DR. KITCHEL: Good afternoon. I am Scott Kitchel. I am a practicing orthopedic surgeon from Oregon, and I am clinical assistant professor of orthopedic surgery at the Oregon Health Sciences University.

My practice is limited to spine surgery and I have no financial interest in any of the spinal implant companies, not am I receiving any reimbursement beyond my travel expenses, for my participation here today.

I appreciate the opportunity of speaking with you today and will be happy to participate in the open session, to answer any questions which my comments may rise.

I would like to thank also the FDA staff and the panel for what has to have been a huge effort in putting together this guidance document.

I have been the principal investigator in IDE studies and have participated in presenting data on several occasions to this panel..

One of my greatest frustrations in these endeavors has been the participation of FDA staff in helping us to

design both the study and the statistical modeling to be used, then performing the study as we agreed to, only to find that the panel presentation that the study design and the end points which had previously been agreed to, do not meet the pleasure of the panel to allow recommendation of device approval.

I hope that through efforts such as this document and today's meeting, and with some further thought and modification, will go a long way in preventing this very unpleasant circumstance.

I would like the chance to address a few specific points within the guidance document, which I believe bear some careful consideration.

The first of these revolves around the end points for a study intended to assess the efficacy and safety of a device to assist in the fusion of the spine.

Clearly, the efficacy end point of any fusion device must be fusion. These are devices to assist in fusion and should not be directly judged on their ability to change a patient's perception of their pain or their functional abilities.

In my reading of the document, it would be possible for a device to contribute to a 100 percent fusion rate, accompanied with a 20 percent reduction in a patient's pain, and a 20 percent increase in their function, and yet

the device would be considered non-efficacious by the standards that are set in this guidance document. This is simply wrong and needs to be further clarified by this body.

The primary end point for efficacy in any spinal fusion device must be fusion. Function and pain are complex and multifactorial variables that are important components of these studies, but should not be considered primary end points.

Improvements in these variables should be evaluated based on comparison of device and control groups, rather than any absolute percentage basis.

Related to this issue is assessment of fusion. No one would argue that the presence of mature trabecular bone, spanning one vertebral body to the adjacent one on a radiograph constitutes a fusion.

However, with the scatter artifact of metallic implants on radiographs, other assessments of fusions must be considered.

I believe the literature validates flexion, extension radiographs, CT scanning, and direct exploration as a means of fusion assessment.

Some incorporation of these diagnostic methods and their results should be included in your document.

The issue of duration of a clinical trial to determine fusion has spawned substantial controversy at

these meetings in the last few years.

My understanding of the IDE process is that the device being examined must be found to be efficacious and safe for the intended use.

In the case of spinal fusion devices, with fusion as the primary end point, this does not always require two years.

In order to prepare a recent manuscript for a scientific article, I did an extensive review of lumbar fusion research, both in peer reviewed journal articles and public information presented to this body.

It is clear from this review that the efficacy of a device to assist in lumbar fusion can be judged at the 12-month point rather than requiring 24 months.

Any further changes beyond 12 months in the rate of fusion is only an increase. Stated more simply, lumbar fusions that are going to occur will likely occur in the first 12 months.

Once the spine is fused, it remains fused. There is nothing to support a notion that a space which is fused at 12 months will be anything but fused at 24 months.

With regard to safety issues, the literature supports a similar conclusion. Device related safety issues are overwhelmingly related to device placement and the immediate perioperative period.

In carefully evaluating the largest four fusion device studies available, there are no new safety issues that occur greater than 12 months following implantation of the device.

It seems clear that requiring 24-month follow up as a blanket policy in all studies is neither logical nor supported in the literature for the IDE process.

There certainly may be studies where 24 months is appropriate, but to adopt this as a one size fits all policy seems contrary to the spirit of the FDA modernization act.

As an investigator and reviewer of this data, I would like to solicit your help in leading us all to a uniform and concise method of reporting complications.

Whether we are to adopt the World Health Organization system, or this panel and the FDA would like to establish their own system, a simple, consistent means for determining what represents a complication and then classifying it as major or minor, and device related or unrelated, would be a giant step forward in the process of investigational device exemption studies.

All pertinent data related to a device should be considered in the IDE process. This is clearly the new mandate to the FDA to allow a more rapid process to clearly evaluate new devices for their safety and efficacy.

Specifically, when a new device being reviewed is

so similar to an already-approved device that it is licensed under the same patent, then the safety and efficacy data for the already-approved device should be considered in the application and evaluation of the new device.

To disregard this data, to maintain market share or competitive advantage for one company over another is not in the best interests of my patients.

Finally, I would like to urge the panel to remain flexible. The guidance document should provide guidance, but not set absolute criteria for every IDE study.

Not all devices can be evaluated in a prospective randomized study. No acceptable control operation may be available in some instances.

Similarly, every device does not require a 24-month follow up in every clinical setting. Some of the longer-term follow up could thoughtfully and appropriately be done through post-marketing surveillance.

Thanks again for this chance to comment, and I would be happy to address any questions in the open session.

DR. BOYAN: Thank you very much. Are there any individuals other than representatives of professional societies in the audience who would like to make a public comment at this time? Industry is also excluded from this invitation.

Seeing none, then we will move on to the next part

of the presentations. We are going to proceed with professional societies presentations.

I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone, as the transcriptionist is dependent on this means of providing an accurate record of the meeting.

We are requesting that all persons making statements during the professional societies presentation time of the meeting disclose whether they have financial interests in any medical device company before making your presentation to the panel.

In addition to stating your name and affiliation, please state the nature of your financial interests, if any.

We have three requests. I would first like to ask Dr. Neil Kahanovitz, an orthopedic surgeon and second vice president for the North American Spine Society to provide his comments on the preliminary background document for IDEs for spinal assemblies.

**Agenda Item: Professional Societies
Presentations.**

DR. KAHANOVITZ: Thank you. My name is Neil Kahanovitz. I am the second vice president of the North American Spine Society. I am a research consultant for Electrobiological, Incorporated.

NASS, the North American Spine Society, has more

than 1,800 members around the world. Of these members, approximately 1,400 are orthopedic surgeons or neurosurgeons who practice in the United States.

These NASS surgeons represent a substantial majority of the surgeons who participate in spinal device IDE clinical trials, and who use the evaluated products after they are approved by the FDA.

Therefore, the guidance offered in your documents has a broader scope than the spinal device industry, but directly impacts our membership.

NASS has responsibility to its membership, as well as the patients of its members, to offer comments which may ultimately shape the document into one which affords sound, scientific guidance.

NASS has some comments which we hope are taken into consideration by the FDA and the advisory panel in the review, further development, and finalization of this guidance document.

These comments are as follows:

The FDA indicated that randomized, concurrently controlled clinical trials offer many advantages over other types of study designs.

However, alternative clinical trial designs, such as the use of non-randomized concurrent controls, respective controls, or literature based controls may be acceptable

even in light of the limitations inherent to these designs.

NASS certainly believes this prospect of randomized controlled clinical trials are optimal, but also recognizes that some products and treatments cannot be evaluated in such studies.

This is especially true if the proper standard of care controlled treatment is not acceptable as a control treatment to the FDA.

NASS also believes that the FDA should recognize the value of the data arising from a prospective, randomized controlled clinical study.

This study design allows direct comparisons to a control treatment with minimal bias. It promotes the reliability of the conclusions and the ability to establish safety and effectiveness of the treatment.

Accordingly, the FDA could base device approvals on data from fewer patients or shorter term follow up if the data are generated in a well-conducted, prospective, randomized, controlled clinical trial.

The safety and effectiveness end points referenced in the background guidance document appear correct, and are consistent with the types of evaluations routinely performed in association with spinal surgery.

We encourage the FDA and the advisory panel to consider the following points in this area.

Evidence of bridging trabecular bone between the involved vertebral end plates is conclusive evidence that fusion is present.

However, detecting the presence of bridging trabecular bone can be difficult, especially in proximity to metallic implants.

If bridging trabecular bone is not detectable radiographically, it does not necessarily mean that fusion does not exist.

In such cases, one should rely on stability measurements and the absence of radiolucent lines. Therefore, NASS advocates that evidence of bridging trabecular bone not be the sole requirement for fusion.

Other information would be useful if available, in confirming the presence of fusion.

In order to help facilitate the detection of bridging trabecular bone, the FDA should accept additional or alternative evidence from other widely used radiological methods such as CT scans and MRI, in addition to conventional radiographs.

These methods can be very valuable in determining the presence of trabecular bone.

The Oswestry disability and Roland Morris disability scale are certainly two recognized and regarded instruments for capturing pain and functional status

associated with lower back pain.

In addition, the use of visual analog scales for measuring pain intensity and duration have been reported. Therefore, recommending the use of these methods is justifiable and appropriate.

However, the FDA should reconsider its position on the necessary level of score improvement in order to be deemed a pain function success.

Requiring a 15-point Oswestry score improvement for success may not be realistic. Oswestry scores can range from zero to 100 points with a lower score representing a better condition.

Even though a score can be as high as 100, which would represent terrible pain and incapacitation, the typical preoperative Oswestry score approximates 50.

To require a 15-point improvement with a starting Oswestry score of 50 would represent a 30 percent improvement, a very high expectation.

As per one of your recommended inclusion criteria, a patient may enter a lumbar fusion clinical trial with an Oswestry score of 30 points.

For patients at this level of pain function, a 15-point Oswestry score change would represent a 50 percent improvement.

Since degree of pain relief is contingent on the

initial level of pain, the percentage improvement may be a relative measure of success.

Thus, establishing a 15-point improvement may be inappropriate and clinically invalid, since prospective randomized clinical trials are recommended.

The best way to evaluate the pain and functional outcomes is to compare the actual measurements between the treatment groups, rather than attempting to classify results as success or failure.

Comparing the mean values of actual measurements or the mean values of changes in actual measurements is more appropriate and informative than comparing distributions of patients who have been classified according to an arbitrary convention.

In the overall success of an individual patient section of the background guidance document, the FDA indicated that overall success should be based on fusion and pain function success.

For spinal devices which are intended to facilitate fusion, fusion is the primary end point. In fact, it should be the only clinical end point.

Fusion is often associated with pain relief, but fusion is certainly not a panacea for all patients experiencing back pain.

Back pain relief is very complex, and obviously

affected by many variables other than fusion status. Therefore, for spinal fusion implants, the most relevant outcome variable is fusion. This factor should be the predominant variable in calculations of overall success.

The background guidance document provides considerable information on classifying subsequent surgical interventions.

However, little information is provided on reporting and classifying post-operative complications.

FDA does indicate that all complications need reporting, but the scope of reporting all complications can be daunting and unnecessary.

For example, pain at the graft site or an unrelated broken arm after surgery should not be considered a complication.

It would be more meaningful to focus on reporting adverse events which are directly related to the underlying disease and the treatment of it.

In addition, the FDA should address the issue of co-mingling safety and efficacy measurements. For example, if a primary effectiveness measurement is fusion, should a non-union be reported as a complication.

Should a complaint of back pain be reported as a complication if it is also being measured in the clinical trial.

NASS recommends that it is unnecessary to consider such events as complications, since they are already being measured independently.

In the duration follow up section of the background guidance document, the FDA indicated that the duration of follow up for devices involved in lumbar spinal fusion clinical trials is a minimum of two years.

NASS believes that the proper duration of post-operative follow up is contingent on the nature of the clinical trial, the treatments involved, and the end points being evaluated.

The duration of clinical trials should not be arbitrarily set.

We believe the FDA recognizes this based on statements in this section which imply that clinical trials involving cervical spine fusion devices and biological products such as BMPs or adjuncts such as electrical stimulation, may have shorter duration.

NASS also supports the FDA comments that a well-designed premarket clinical trial in association with a post-market study may allow for shorter premarket clinical trial duration.

For clinical trials involving spinal fusion devices, both lumbar and cervical, the safety and effectiveness can be adequately established long before two

years following surgery.

The primary end point for these trials is fusion, and fusion typically occurs in the lumbar spine within 12 months of surgery, and in the cervical spine in approximately six months following surgery.

From a safety standpoint, a majority of the complications occur either during surgery or shortly thereafter.

Therefore, shorter term, premarket clinical trials, followed by supportive post-market data is a reasonable approach to make new technologies available without placing patients at undue risk.

NASS appreciates the opportunity to comment on the guidance document and hopes that the FDA will consider our comments in preparation of the final guidance document. Thank you.

DR. BOYAN: Thank you. We would next like to invite Dr. Richard Fessler from the American Association of Neurological Surgery and the Congress of Neurological Surgeons to provide his comments.

DR. FESSLER: Madam Chairman, I am Richard Fessler. I am the Dunsbar Dalton Professor of Brain and Spinal Surgery at the University of Florida, immediate past chairperson of the joint section in disorders of the spine.

I am also a consultant to a medical manufacturer.

Prior to embarking on the practice of medicine, I worked as a basic scientist for many years, a PhD in neuropharmacology and primary emphasis on the neuropharmacology of pain sensation, and as a master's in psychology with a primary emphasis in biostatistics.

Today I represent the American Association of Neurological Surgery and the Congress of Neurological Surgery and over 4,500 neurosurgeons in the United States.

We wish to thank the FDA for providing us with the opportunity to review this document and to comment on the referenced guidelines.

Neurosurgeons are dedicated to treating patients with spinal disorders, to participating in spinal device IDE clinical trials, and we also utilize the evaluated products after the FDA approves them.

Therefore, this guidance document is very important to us, as it directly affects us and our patients.

We believe the guidance document is an excellent document. It is well researched and, on the whole, scientifically and medically sound.

Nonetheless, the AANS and CNS have some comments that we hope will be taken into consideration by the FDA and the orthopedic and rehabilitation panel prior to finalizing this document.

Our comments are organized to follow the outline

of the documents, or the topics discussed, in the document.

Under the investigational plan and study design, the FDA has indicated a preference for the use of randomized concurrently controlled studies, stating on page 9 that, "the use of randomized concurrently controlled studies provides many advantages over other types of study designs."

While the AANS and CNS acknowledge the clear superiority of this design, we also recognize that many practicalities often make these designs impossible to achieve.

For example, extreme variability in disease processes, small sample sizes, concurrent illnesses, and inability to blind the patient and the evaluator of the knowledge of the treatment arm, make valid randomization nearly impossible.

Furthermore, randomization to a group which historical data might suggest is inferior to the early results of a new procedure could, under some circumstances, be construed as unethical.

The AANS and CNS therefore strongly urge the FDA to allow appropriate flexibility in research design.

Under the inclusion criteria for lumbar degenerative disc disease, the FDA clearly recognizes the complexity of defining signs and symptoms associated with degenerative disc disease in the discussion and

recommendations on pages 12 and 13.

The attempted definition of degenerative disc disease on page 13, however, unrealistically classifies degenerative disc disease with "'discogenic pain," an even more controversial and poorly understood concept.

The AANS and CNS feel that an alternative approach may be more useful and recommend the following changes to the document.

First, eliminate the term discogenic entirely. Include back pain and reticular pain as useful in the diagnosis of degenerative disc disease.

In addition to history and radiographic studies, physical examinations should be considered in the diagnosis of degenerative disc disease.

Include the vacuum phenomenon in the radiographic factors of degenerative disc disease, and include myelography and discography among the suggested radiographic measures.

Finally, the document suggests that, "ideally, the patient should demonstrate failure to improve with conservative non-surgical treatments for a period of at least six months."

Requiring a full six months of non-operative treatment as part of a trial is ideal, but often difficult to obtain.

Studies have shown that six months of conservative treatment such as physical therapy, injections, epidural blocks, bed rest and pharmaceutical treatments is too long. Payers also will not cover that extent of treatment.

We suggest a three-month non-surgical treatment period. This period of treatment would eliminate the patients who would improve spontaneously.

Under the section, duration and follow up schedule, the guidance suggests that a two-year follow up period is required to determine whether a fusion has taken place.

The AANS and the CNS believe this is too long and strongly recommend the panel to adopt a 12-month follow up period to determine a solid fusion in the lumbar spine, and a six-month follow up period to determine solid fusion in the cervical spine.

Rarely does pseudoarthrosis develop after one year in the lumbar spine and six months in the cervical spine, if there was a solid construct at the end of those periods. Consequently, a shorter follow up is more appropriate.

Furthermore, duration of follow up should be based on the type of clinical trials, since clinical trials involving cervical fusion devices and biological products such as BMPs may have shorter follow up time frames.

Under the fusion/non-fusion status, evidence of

bridging trabecular bone on X-rays is an ideal method of judging a fusion. However, it is often difficult to see because of implant artifact.

Alternative diagnostic methods such as CAT scan, MRI and bone scan should therefore be considered for evaluating whether a fusion is successful.

Under pain and function, the AANS and CNS feel strongly that pain, although acceptable as relevant clinical data, should never be required clinical data.

Pain is a complex, behavioral, physiologic entity which may or may not respond favorably to successful fusion for any number of reasons, possibly not even related to the surgical procedure per se.

Therefore, we recommend that fusion, not pain, be the primary measured variable.

If pain is elected to be reported, then we recommend that any validated measure of pain be acceptable for data reporting.

Finally, because of the relative independence of pain and the pain response variability from a successful surgical fusion, the AANS and CNS recommend that arbitrary success criteria not be stated in this document.

Instead, we recommend that results of appropriate statistical analysis be reported, but not judged on the basis of an arbitrarily determined success criterion.

Again, the AANS and CNS thank the FDA for seeking our input to this guidance document. We commend the FDA for an excellent draft.

We agree with most of the points presented in the document and we hope the FDA will consider our comments in preparing the final document. If you have any additional questions, we would be very pleased to participate in that. Thank you.

DR. BOYAN: Thank you. We have -- the third presentation is from the American Academy of Orthopedic Surgeons. They had identified Dr. Bernie Stilberg as being the representative. Is Dr. Stilberg here, or another representative of the Academy?

MR. LUBBUCK: I am Dave Lubbock(?), the deputy director of the Washington office of the American Academy of Orthopedic Surgeons. The American Academy of Orthopedic Surgeons may participate later, but we have nothing to present today.

DR. BOYAN: Thank you, Dave. All right, then, at this point we are going to move on to the industry presentations.

We have three requests to speak. We will begin with -- our first speaker will represent OSMA, the Orthopedic Surgical Manufacturers Association. It will be John Dichera.

Agenda Item: Industry Presentations.

MR. DICHERA: My name is John Dichera. I am employed by Helmedica Incorporated. However, I am here today speaking on behalf of the Orthopedic Surgical Manufacturers Association, or OSMA.

All members of OSMA are manufacturers of medical devices used in orthopedic surgical procedures.

OSMA's goal is to make orthopedic surgical devices available for patients' needs, with minimal delay.

To achieve this, OSMA participates in standards development, FDA interaction, patient education, product labeling guidelines, and cooperation with health care professionals.

OSMA appreciates FDA's efforts in preparing this draft guidance document for IDEs of spinal assemblies. The intent of providing guidance or a road map to designing and conducting clinical trials of spinal devices has considerable merit.

The quality and fairness of FDA's document should abet the industry's efforts in gaining approval for new products.

Since OSMA's membership includes the spinal implant industry leaders, it was incumbent on the organization to voice a position and comments on this draft guidance document. We appreciate the opportunity to do so.

OSMA believes that the document, en masse, provides adequate guidance. However, there are some guidance points that require special emphasis and possible modifications.

First and foremost, OSMA wants to underscore that flexibility in clinical trial designs must be maintained.

Even though there is a common thread among spinal assemblies, there are enough differences in these devices and their intended uses to not have the one size fits all criteria.

Often guidelines become law, and companies succumb to them in order to get their IDEs approved. This stifles creativity and thwarts any attempts to make the process more efficient.

With respect to flexibility, FDA has encouraged the industry to sponsor clinical trials having a prospective randomized control design.

Without a doubt, clinical trials of this design have the greatest scientific appeal and, if properly conducted, they can provide powerful supporting evidence.

However, for surgical implants, prospective randomized controlled clinical trials are very difficult, if not impossible, to conduct.

This is especially true if no suitable control procedure exists. Many of our member companies have

received strong recommendations from FDA to support such trials, and have found them very slow.

This slowness is due to reluctance by surgeons and patients to participate. In addition, for the surgeons who do participate, their enthusiasm to recruit patients wanes once they detect a seminal difference in the outcomes of the treatments.

It then becomes an issue of medical ethics, and the surgeons will abandon the inferior treatment, typically the control.

As a result, there are insufficient data to readily support the product approvals, and the whole IDE PNA process stalls at best, and often dies.

Further, if the device is already marketed for another diagnostic indication, surgeons may use the device off label, because they believe it will make a clinical difference for their patients. However, such uses can present issues, including liability.

OSMA is encouraged by FDA's recognition in the guidance document of alternative clinical trial designs.

It reinforces a position which has already been confirmed in 21 CFR 860.7, which states that valid scientific evidence may arise from a number of sources other than well-controlled clinical trials.

We recognize the inherent limitations of such

designs. However, they should be available if the need arises and if their use can be justified.

Stated another way, FDA should not mandate that clinical trials have a prospective randomized controlled design.

Next, OSMA wants to emphasize statements made by FDA in the document regarding the duration of clinical trials.

As a possible alternative to the FDA's and the panel's historical viewpoint that two year follow up data are necessary to support product approvals, FDA offered that post-market studies could augment pre-market studies to shorten the duration of pre-market clinical trials.

For example, a traditional lumbar fusion device may gain approval with 12-month post-operative follow-up data followed by a post-market surveillance study that would continue this evaluation period for an additional two years.

The FDA modernization act encourages methods to foster timely approvals, and OSMA supports this concept.

Also, with regard to clinical trial duration, OSMA agrees with statements that the length of clinical trials should be contingent on the nature of the devices under evaluation.

For example, clinical trials of cervical spine fusion devices should be of shorter duration, perhaps

requiring only six months or at most one year post-operative follow up data, since the literature shows that cervical fusions occur within this time frame.

Other areas of the document which deserve mention, with the hopes of spurring panel discussions are the following:

The first pertains to the radiologic methods used to determine fusion. FDA has indicated that fusion be based on traditional methods. If other methods, such as CT and MRI are used, sponsor must provide validation.

OSMA believes that CT and MRI are mature technologies, that they offer advantages over conventional X-rays, such as the ability to detect the presence of bone in places in which it may not be possible by traditional means. They should be considered as an adjunctive means of supporting a fusion decision.

Another area for panel discussion is FDA's criteria for pain and function success. These criteria are far too stringent and will lead to misleadingly low success rates.

For example, for the numerical analog scales, FDA indicates that the improvements had to be at least two points from baseline.

This represents a change of 20 percent provided the pre-operative score is 10, the worst possible value. If

the pre-operative score was six, a two point change would represent a 33 percent improvement.

With this backdrop, OSMA would like to understand FDA's basis for these criteria.

Also, OSMA encourages FDA and the panel to consider that success be based on the percent improvement from baseline, such as five percent or 10 percent.

The third area for discussion pertains to the number of patients being contributed by each investigational site in the clinical trial.

FDA said that each site should recruit at least 10 patients per intended use of a treatment group. For the simplest concurrent clinical control trials, each investigational site would be expected to enroll 20 patients.

Depending on the intended use of the device, this number of patients can be exceedingly high. Our companies have had many situations where sites would need a year or more to recruit this number of patients.

The cynic would say that there is need to do a better job of picking investigators. However, it is not that easy.

Clinical trial inclusion and exclusion criteria can be so restrictive that only the largest referral centers can meet this quota.

As a result, many good investigators are overlooked on the basis of numbers alone.

Also, this sample size convention invariably leads to a prolonged patient recruitment phase and an unduly long clinical trial.

OSMA advocates the number of reduced to five patients per intended use per treatment group at each investigational site.

In conclusion, OSMA's parting message is that the guidance should respect clinical design flexibility and promote efficacy, thus leading to shorter durations.

We want to thank the FDA, again, for their insights and efforts in preparing this guidance document, and for determining and conducting clinical trials for spinal assemblies.

We also thank the panel for their efforts in reviewing and shaping it. OSMA representatives in the audience, in addition to myself, would be glad to answer any questions that you may have. Thank you.

DR. BOYAN: Thank you. The next speaker will be from Sophomore Danig(?). Dr. Trehorne?

DR. TREHORNE: I am Rick Trehorne, and I am employed as the vice president of research and regulatory affairs at Sophomore Danig.

As a major development of spinal implants,

Sophomore Danig appreciates the opportunity to express its opinion on the proposed guidance document for spinal devices.

In our opinion, over the years, the FDA has been expecting more and more from spinal fusion devices, more than they are designed to do.

Spinal fusion devices are used to aid the fusion process and hopefully to reduce pain. As you have heard from several speakers today, successful fusion does not always eliminate or even reduce pain.

Pain is a subjective opinion, affected by activity, drugs and, as several studies have reported, dependent upon whether the patient is involved in litigation or has a Workman's Compensation claim.

Because of this, Sophomore Danig advocates that there only be one primary end point for an IDE clinical trial of a spinal fusion assist device. That end point is fusion.

Alleviation of pain may be a legitimate expectation of the spinal procedure, but not of the device.

Don't get us wrong, though. The levels of pain and function should certainly be evaluated in an IDE clinical trial of a spinal device, but as secondary end points.

Also, one should expect that the fusion treatment

should not worsen the levels of pain and function. However, to expect and to require and to base an implant's success and product approval on significant pain relief and function enhancement is beyond the expectations of the device.

The FDA is trying to require that patients show marked improvements in pain and function in order to characterize the device as a success.

As such, the FDA is regulating the procedure and the practice of medicine and not the device.

If fusion is the primary effectiveness end point and the true indicator of the success of a device, the duration of follow up in clinical trials could be dramatically shortened, since fusion or the lack thereof can be readily determined at post-operative time points shorter than 24 months.

For lumbar procedures, this time point is around 12 months and for cervical fusion, six months.

We also encourage you, the panel, to encourage the FDA to be receptive to new imaging and statistical modeling techniques that can increase the accuracy and certainty of early conclusion of clinical trials.

We would like to now briefly highlight some other issues that need further consideration in this document.

First, the FDA has traditionally prescribed that patients be evaluated in the IDE clinical trial up to 24

months and then biannually thereafter.

The guidance document before you changes biannual to annual. This change places a substantial burden on the sponsor and clinical investigators without any perceived benefit.

Second, in the statistics section, the FDA indicates that the number of patients in a clinical trial be based on the ability to detect clinically and statistically significant differences between treatment groups.

This language appears to imply that all clinical trials should have a superiority design.

In actuality, clinical trials are designed to show statistical equivalence. We recommend the guidance document be amended to reflect this.

Finally, and most importantly, the FDA proposes requiring pilot clinical trials for new spinal device designs and investigational protocols.

As the guidance document says, spinal devices are unlike IDEs for most orthopedic implants.

Does this panel agree that spinal devices are unlike other orthopedic implants. Does it agree that pilot studies should be performed for "new" spinal devices.

We believe the answer is no. If the patients, physicians, IRBs and companies are all willing to take the risk of performing a pivotal trial, we believe that the FDA

should not force a pilot study to be performed first.

In a spinal pilot study clinical trials we have performed so far, it seems as though the FDA wants us to prove that the devices are safe and effective before being allowed to proceed to a large scale pivotal trial.

Of course, it is only through a large scale pivotal trial that safety and effectiveness can be demonstrated.

This conservative position on performing pilot studies on spinal devices can delay device approvals by two years or more.

We ask this panel to give the FDA guidance on its view of whether spinal devices should be treated differently, and when to require pilot trials.

In conclusion, we appreciate the FDA's work in preparing this document. We would ask that prior to finalization, we would ask that the FDA reissue the document, again, for comments. Thank you for the opportunity to voice our opinion.

DR. BOYAN: Thank you, Dr. Trehorne. The final speaker that has identified themselves in advance is Dr. Martin Persenaire from DePugh Acrimed.

DR. PERSENAIRE: Good afternoon. My name is Dr. Martin Persenaire, and I am the vice president for clinical affairs at DePugh Acrimed.

I also thank the FDA and the panel for the opportunity to give some comments on the first draft -- although I understood it was not even a draft -- guidance document as yet, to come to uniformity of clinical trial design.

I think the very positive aspects of the initiative that FDA has taken is that, indeed, we will move toward a uniformity of design and, with that, a comparability of results that will make it easier for both the FDA as well as the medical community to make scientifically based judgements on which treatment might be appropriate for which patient.

At the same time, I would like to warn against making the document too rigid and too detailed, allowing no more flexibility to accommodate different implant designs or patient groups.

I will forego a number of the notes I made, because previous speakers have already addressed some of them, even multiple times, underscoring their importance, but I would like to highlight a couple of points.

First, I think with all of you, that a randomized prospective study is the best type of design, provided it is double blind.

We all know that in surgery double blindness is impossible. With that, surgeon bias is inevitably

introduced.

Also, the result of a certain device is not only dependent on the device itself, but also on the experience, comfort and skills of the surgeon using that device.

By preferring a concurrent trial design, we can ensure that only surgeons that feel comfortable with a certain device, as well as with the technique required to implant that device, will use it.

Therefore, we will not run into the problem which might come up in a randomized study, where the surgeon would feel less comfortable with the control treatment.

On the trade off, I think in the surgical design, a concurrent study might be scientifically as valid as a randomized study.

A couple of details that have not been mentioned here, FDA made a rather lengthy list of exclusion criteria. If I go to possible exclusion criteria, it appears that people who smoke, are on Workers Compensation, that have more than two level disease or are obese should not be included in studies because they kind of may fudge the picture.

Depending on which country we are, that may be an exclusion of anywhere from 20 to 80 percent of patients.

I think that for a device to be evaluated, we should try to include as many of the future patients as

possible. Otherwise, extrapolation of the results to the actual daily practice of the physicians will be very hard.

If we come back to the example of the obesity, in this case the recommended scales to use were the Metropolitan Life table or the body mass index scale.

There I wondered for a moment why those were used. The patients identified at risk in those scales were identified at risk based on cardiovascular disease incidence, not on osteoarthritis disease.

I am not sure, since there is evidence presented in the literature, that it was the increase in weight, the incidence of back problems also increases, that it makes sense to exclude patients based on a risk profile for one disease, for treatment for another disease.

I would also ask the panel if they have recommendations as to what level of obesity should be an exclusion criterion for spinal treatment.

Lastly, the criteria FDA presented for degenerative disc disease, indeed as Dr. Fessler already presented, seemed to be incomplete and somewhat arbitrary, especially the requirement that the disk space should be reduced by two millimeters is something which I cannot see how you can evaluate that objectively on a first patient visit.

I will conclude my remarks here. All the other

points I have on my list have already been made. I again thank FDA for making the effort to come to a uniform approach to spinal studies. We are more than willing to engage in discussion in the future on the final document. Thank you.

DR. BOYAN: Thank you. Are there any other representatives of industry that would like to come forward and make comments before we move on?

Seeing none, we will now move on to the general panel discussion.

Agenda Item: Preliminary Background Discussion.

Panel Discussion.

DR. BOYAN: We are going to begin the discussion with presentations by Dr. Yaszemski and Ducker. I am holding all questions to the end of these so that we have them as a body.

At the end of Dr. Ducker's presentation, so that everybody can plan ahead, I am going to permit a five-minute break.

DR. YASZEMSKI: I would like to separate my comments into two groups. I am going to first start by addressing each of the global issues that were presented in the panel questions handout. Then I am going to make comments regarding several points in the guidance document itself.

I will make these comments for two purposes, one to perhaps raise the issue so that we can have a discussion about the things that I feel are important in this document. Occasionally, some of the comments will be in the form of suggestions themselves.

With respect to the first global issue, whether there are other instruments available for outcome measures, I might mention that representatives of the societies, two of whom have come to the podium today -- that is, the North American Spine Society and the American Academy of Orthopedic Surgeons, have outcomes instruments.

NASS has an outcome instrument and the AAOS project has an outcomes instrument. Also, the Scoliosis Research Society has an instrument specifically devoted to deformity.

That may not be the most appropriate one here, but my point is that we should consider instruments that have been developed by societies whose members have given much thought to this.

I am not aware of whether the AANS or the CNS has similar instruments. Perhaps during the discussion we can ask Dr. Fessler if he is aware of them, and we can consider those, too. I imagine Dr. Ducker may also know about those societies' contributions to outcomes instruments.

The study end points are patient reported or

imaging reported. I am going to get to that below. I just want to bring that up now, that I will have some comments to make about that.

The question also mentions whether cervical and lumbar should be considered separately. I agree with that.

I would also suggest that from a semantic perspective we change lumbar to thoracile lumbar, to include those cases where the instrumentation may be applied also to the thoracic spine, and that we recognize that sometimes the fusions go to the sacrum and to the pelvis. Perhaps objectively, or just in an assumed fashion, give discussion to how to evaluate those instrumentation constructs that pass the lumbosacral junction and pass the sacroiliac joints.

The second question, or the second global issue relates to radiographic end points for fusion. I think we should give consideration to discussing criteria dependent upon the goal of the fusion, be it an anterior fusion, a posterior lateral fusion, or a combined anterior and posterior fusion, and discuss what the appropriate study end points for fusion success should be in each of those instances.

As an example of what end points should be, whether they should be considered clinical and patient reported or based upon radiographs, I offer the following.

Give consideration to the presence of the radiographic successful posterior spinal fusion, if the patient reports that they still have pain.

In this instance, perhaps, anterior degenerative disc disease or some other soft or hard tissue abnormality may be present to explain the patient's pain.

The device may have been effective in bringing about the fusion and the pain will persist because of the contribution of some other anatomic structure.

I suggest we exercise caution in attributing pain relief to an implant. I would offer that perhaps the word "effective" in the instance of spinal fusion devices should be synonymous with "fusion."

Tomography wasn't mentioned as a way to assess fusion success of these devices in the guidance documents. I recognize that some radiology departments are phasing out their tomography machines, but I suspect that it would be worth a few moments of discussion, especially from our radiology colleagues, to discuss whether tomography might be a feasible way to do things.

I do feel that reformatted CT is probably highest on the list of appropriate ways to assess the fusion mass. For the different types of fusion, it would perhaps be appropriate to give consideration to the expected orientation of the trabecular bone in the fusion mass to the

plane of the CT machine, and attempt to assess the utility of this radiology method for each of the different types of fusion that we are likely to encounter.

Global issue three refers to restoration of body height. I would think that if the surgeon feels that reattainment or increase of body height is an important thing and he or she attains that at surgery, then the guidance document's recommendation of maintaining that height plus or minus some number, and two millimeters was suggested is an appropriate end point.

The height changes, however, would be expected to occur only during the period of graft incorporation. If the height changes but subsequent solid fusion occurs, then the changing height potentially wouldn't be a concern unless, of course, it was associated with some deformity that the surgeon might feel itself was responsible for continued pain.

Global issue number four speaks to assemblies not intended for fusion.

I would like to begin my comments on this global issue by bringing up the fact that disc and nucleus replacement devices are newer than those devices intended to facilitate fusion and, hence, more if you will, experimental in nature.

When looking at these devices, I suggest we

discuss the potential contributions of arthritic facette joints and other soft tissue structures to the patient's problem and discuss how we are going to separate out the effect of the disc and its replacement from contributions to the patient's pain from those other structures.

As an example, perhaps this concept of disc replacement is in some way parallel in the knee to a unichondral arthroplasty or a total chondral arthroplasty without patella resurfacing, in that we are not addressing all parts of the functional spinal unit when we are replacing the disc.

The other part of global issue number four refers to appropriate control groups. My suspicion is that this is going to be an item that engenders much discussion. So, I will say just a little about it and then leave it open for the rest of the group and industry and academia representatives to discuss further.

Perhaps a potential control treatment combination in this instance might be single level degenerative disc disease with minimal facette arthritis, and comparison given to a disc replacement versus non-operative treatment.

One could then an observable end point as a change to a different treatment.

Global issue number five relates to metastatic tumors. I think metastatic tumors represent a fundamentally

different problem than the fusions we have been discussing up to this point.

I think we need to consider the tumor biology, whether it is radiosensitive or radioresistant, whether effective chemotherapy exists for the particular tumor in question, and whether the metastasis is osteoblastic or osteolytic.

We need also to consider the surgical goal, whether it is pain relief or the preservation or improvement or neurologic function and whether that can be obtained by non-operative means.

Should the surgeon choose surgical means, does the bone present have adequate density to anchor the instrumentation.

The issue of life expectancy is a difficult one. Life expectancy, I believe, is difficult to predict and we should give consideration to not denying oncologic patients a surgical alternative for stabilization and potential pain relief if non-operative means are not successful.

I respectfully submit that we discuss the less-than-three-months clause in the guidance document, and I would recommend allowing surgeons and patients to decide upon surgical therapy, if they agree with each other that it is the appropriate thing for that particular patient.

In an oncologic patient, as opposed to the prior

fusion patients, perhaps a link between instrumentation and pain relief is appropriate, because perhaps the stabilization of the pathologic fracture afforded by the instrumentation will be the only stabilization that that patient has if, for reasons of longevity and host issues such as radiation and nutrition, a fusion never occurs during the patient's remaining life.

Issues six, seven and eight, I think we should give consideration, as I mentioned earlier, to the separation of pain relief and a specific device. Perhaps the selection of procedure might be more appropriately linked to patient reported outcome and device effectiveness linked to the attainment of fusion.

I would like to finish now with some comments specifically from the document. On pages five and seven, perhaps we should give consideration to discussions with the Center for Biologic Evaluation and Research and the Center for Drug Evaluation and Research, to include their concerns and recommendations in the guidance document regarding composite devices, into one document, for those drugs and biologics likely to be used in spinal assemblies.

On page seven, ASTM-F-1717 is recommended for pedicle screw systems. I believe we should consider including similar mechanical testing guidance in the document for anterior spinal systems.

On page 7 and page 16, specific numbers are given per group in mechanical testing and in patient studies. I believe we should give consideration to expanding the guidance document by including the power analysis and the values of alpha, beta and delta that went into producing these recommended numbers.

As a conclusion, I think that specific guidance is a reasonable thing and is good to do, with the caveat that, as the document suggests, it remain a living document and subsequent to alteration, change and improvement as new issues and new information are garnered by industry and academia. Thank you.

DR. DUCKER: I appreciate the formal presentations. I hope mine is a little bit more relaxed. I know we heard from a lot of PhDs and maybe some SOBs.

Trying to get this into a working sort of document, from the perspective of a practicing neurosurgeon who has been on some editorial boards, does a journal, I can appreciate very much what Dr. Zdeblick pointed out as to a moving target when you set out to do studies for any government regulation or any government agency.

For that reason, to simplify the document would be one of my requests, where you basically have the same kinds of systems without concrete determinations of what you expect at each one.

Our evolution for clinical assessments has obviously changed in the last five years. What we think is important may change again in five years.

I would plead that that be part of it, especially with the confusion that many people perceive many things in Washington.

In a particular study, my initial plea was that it be brought a little bit closer to evaluation of drugs. I know not everybody agrees with that.

Basically the first phase of a drug study is its safety. If you are going to put in a new device, you put it in a few select patients, and those are the ones that you continue to follow.

If it indeed is safe and appears to be doing everything that you think should happen in general, to prove its effectiveness or at least its equivalency, you would go into a phase II study with a larger number of physicians and patients.

I am in complete agreement that, as ideal as it is to randomize in surgery with devices, it is simply not possible.

I have tried different programs and you run into various physicians' beliefs, which border on their religion, as to how much they should or should not do in a particular case.

More important is to have a good outcome assessment tool, one of which you can count on that you can measure -- in this case mostly fusions.

I have to point out, for this document we are also going to get into, sooner or later, artificial discs and artificial replacements, where fusion is not the end point.

If you have good outcome tools which have been developed in the last decade which are specific to the problem for spinal disease, these are the ones that you need.

I think writing down exactly one that you have to use is going to backfire. It is equally important to use some kind of SF12 or 36 or whatever one you want, but that is not necessarily the end point. You want specific end points for the function.

This morning we all met to deal with a problem with the hand. I am not sure that an SF36 would have told us anything about that.

I think we need to deal instead with a very focused -- and this would be true for spine. You would have a focused outcome system, and that is going to be true no matter what your device is.

If you go through a similar drug system where your phase I, phase II and in phase III which would be different from drugs, I think the manufacturer should have the right

to sell it and monitor it.

I don't think it has to be as bad as we say. It can clearly be done quicker than what we say. I am in agreement with everybody's statements, that after a year, for spinal devices or spinal surgeries we pretty well know what is going to happen.

There is data to be released from Drs. Mandama and Long at Hopkins with an NIH study that you all have not seen, but I will bring it to you, in its pre-form, where they monitored about 3,000 patients in eight different medical centers, treated both by neurosurgeons, orthopedic surgery, where they were treated with surgery. Roughly about 15 percent of the population had an operation.

The important thing to know is that after a year, by far those that were going to achieve their improvement, that was a fact, and very little improvement between one and two years.

The only patients that were slower to get well basically were those that had a disease for a long time, and if you had it for two or three years, it would be longer.

With those thoughts in mind, we can go through when we come back, rather than answer all of the nine points that were put to us.

My plea is pretty straightforward. It is, a, we simplify the document with less concrete definitions of what

we expect in improvement.

For example, the Oswestry's scale, I completely agree with everybody else's comments. The Oswestry scale, it just depends on where you enter in, the point where you are going to improve.

There are many other instruments or questionnaires or devices that we are going to use. I think, while that is not necessarily always the end point, it is an important part of it.

We have to include that part of it, especially when we are going to look at non-fused devices, like assemblies for artificial disc and joints.

My concern was to make it simpler and more parallel to the drug system. Thank you.

DR. BOYAN: At this point, we are going to take a break. When we come back, I would like to invite all the people who made presentations to come forward so they can participate in the general panel discussion.

There are only three chairs at this table here with the microphone, but there were more than three speakers.

If the first row behind the microphone could be for the people who made presentations, that would facilitate the discussion. Thanks. Five minutes.

[Brief recess.]

DR. BOYAN: The point of the general panel discussion is actually to have the panel discuss the presentations.

I have invited the speakers to come forward only if it is really necessary, and so that they can be convenient to the microphone.

It is not anticipated that you would offer information. It is just that you are there as a resource, should you be needed.

I would like to ask the panel not to start asking the speakers questions. The goal here now is to get your impressions out for the FDA's use in drafting their guidance document.

I would like to ask Dr. Hanley to start the discussion. Then after Dr. Hanley, we will go the other direction, next to Dr. Naidu and then so forth around the room.

This now, we will go around and any general comments that you would like to make. We are not going to right now specifically address the questions, but we are going to make general comments.

DR. HANLEY: Thank you. Ed Hanley, Charlotte, North Carolina. I am an orthopedic surgeon specializing in spine.

I would like to open up by saying I was very

pleased to see the document. I think it reflects a lot of hard work on many people's behalf at the FDA. I would also like to echo the comments of others that this is a beginning and should not be interpreted as anything other than that, from my viewpoint.

I was also very pleased to see the similarity in everybody's comments. I think individuals from industry, individual physicians commenting, representatives of the specialty societies and members of the committee had very similar comments, I thought, all of which had some validity, and hopefully could be worked on a little bit in our discussion.

I would first like to comment on the randomized, double blinded control ideal study group. We have tried to do that. I think it is almost impossible in most instances.

There is a rare occasion where you have similar treatment modalities, that nobody knows the best one to do and you might be able to do that, but I think it is very uncommon.

I think to hold any one group or study to that criteria would be difficult and no one would pass the test.

I do think, however, we should shoot for some type of concurrent controls when we do these studies. They don't necessarily have to be randomized, but at the same time, at the relatively same place, meaning in the same culture.

I would agree that all the comments about CT as an assessment for radiographic fusion is correct. I don't think we need all those other tests. I think in instances where it is unsure, the study may want to incorporate those other criteria such as flexion, extension and so on. Generally speaking, CT is the standard.

Of course, that may change as time goes by. We should allow for changes in the way we assess fusions.

A difficult issue is that of the evaluation end points. Most things we as physicians treat are based upon the patient's symptoms and findings.

If we do a study of headaches, we generally assess the effectiveness of the treatment on how good or bad the headache did afterwards.

The usual indication for fusion for back pain -- with a few exceptions; there are exceptions -- the usual indication is back pain, or back pain and lower extremity pain or neck pain and upper extremity pain, but it is a pain thing.

The purported method to deal with the pain is to immobilize the space or replace the painful offending thing which, in the spine, sometimes is the disc.

I think to toss out pain and function as outcome measures completely probably is inappropriate. I do recognize, however, that fusion is what the device is

intended to achieve. I think the middle ground there is probably appropriate.

I don't think you can have all one or the other. Obviously the ultimate goal, if you are trying to achieve a fusion to relieve pain, is to accomplish that.

So, some way that is appropriate to measure fusion and to appropriately measure pain and function after a procedure, relative to before the procedure is probably the right way to go.

I don't think we need to be strict and apply 1998 or 1995 outcome measures to this. Rather, let the people who create the study and conduct it use their own measures for their own needs.

I have mixed views about this two-year follow up. I am open to suggestion about it. In the total joint world, we have used pretty much as the standard for implants in orthopedic surgery to assess them, with regard to how patients will do, the thought being that if you make it two years with a joint replacement, you are generally speaking going to do reasonably well.

That is a historical thought, mostly anecdotal thought, I think, but that has become sort of the standard.

That has been my view in the past, but I am certainly open to different ways of looking at it. If it can be clearly shown that you are what you are at six months

or you are what you are at a year, if that can be shown to be true, I think we should be able to deal with that.

I will back off philosophically on my historical perspectives, if someone can show me that that is a reasonable thing to do.

One thing that wasn't discussed -- I will make up a new word now -- the poolability of data from different diagnostic categories.

I think this has been a large problem in the analysis of spinal surgery and spinal surgery utilizing implants.

The reasons patients come to doctors with different diagnoses are different. A patient with ismic spondylolisthesis is far different from a patient with degenerative spondylolisthesis, different age groups, different symptoms, different bone stock, different everything.

Likewise, a herniated disc patient can't fit into that category, nor a tumor nor a trauma patient. I think when data is analyzed with regard to implants or spine surgery outcomes, the study should be created such as to try to get similar groups of patients analyzed by similar techniques and try to eliminate this pool problem that we have had with implants.

Likewise, I think that some discussion -- and I

don't know the right way to discuss it -- but some discussion be held on this large, very ill-defined category of so-called degenerative disc disease.

If you ask 1,000 people on the street or 1,000 spine doctors what it means, you get 2,000 different opinions.

It ranges from the normal aging of a human being to a severe disease that one can easily see on a radiograph. The truth is probably somewhere in the middle.

I think that disease category, if you want to call it a disease, if it is to be studied, it needs to be well defined, as patients enter the study and leave the study.

There is a big difference between someone who comes in with some degenerative changes on their radiograph, traction osteofice, disc space narrowing, old age, and achy back discomfort, and that is all they have is plane radiograph before surgery, and another group of individuals who have a definable back pain with MRI changes, concordant discography, one level disease and a younger age group.

These are different problems. I am not saying one is better than the other, but I think we need to deal with that -- I will use the slang -- garbage can diagnosis.

I am not sure that I have all the answers, but I think we at least need to address it.

Lastly, I would like to agree with Dr. Ducker,

that the simpler things are, the easier they are to understand, the easier they are to carry out. We don't want to be too rigid in this thing.

Let's try to establish some broad guidelines, let investigators use their judgement and have this thing, as Dr. Yaszemski has said, have a little life to it, or be a living document. Thank you.

DR. NAIDU: Sanjiv Naidu. I am a hand and upper extremity surgeon. I will defer further comments to my statistician colleague next. I think all my concerns have been addressed previously by the various speakers. Thank you.

DR. LARNTZ: Kinley Larntz, and I am a statistician. A few points. I believe in randomized trials.

I think they are very important to try to do, and I think that they can be very successfully done.

There is a very critical and important point. If there isn't equipoise between the arms, they become incredibly difficult to do.

So, it is true that if there are not people who believe in the control arm, it is going to be real hard, no question.

So, it can be done, should be done. If it can't be done, then, with considerable thought, there are lots of

other designs, and the document addressed that appropriately.

Let me say, from a statistical point of view, a randomized control trial is actually simple, from a statistical point of view. It is simple.

The further away you get from that, the more you have to employ statisticians, and I am in favor of that. That requires a good bit of work.

By the way, I have to say that the ideal control, if I were setting up a study and I was going to evaluate a device, the ideal control situation for me, here are the two arms.

Use this device the best you can versus do everything you can, but you can't use the device. That is my study, my ideal study.

You have got this device. You can use it as best you can. If that device is not available to you, that is the control arm. So, that is what I think the ideal two armed study would be.

I think it may wind up that the control is a bit of a mixed bag, but patients are a bit of a mixed bag, aren't they?

Shouldn't we do the best for the patient as our control? By the way, you are going to do the best for the patient with the device, too.

Small point. I have talked -- there has been a discussion about these scales, and how look at these scales and should you have a two point difference for success or not.

I am actually quite in favor of analyzing the scales as continuous scales. It may be that it is convenient to say that a certain point improvement amounts to real improvement, but there have been a lot of points and it depends on where you start.

All those are valid, but you have to analyze them as a continuous scale. I did a little calculation. It turns out that at least if the scale is normally distributed -- which nothing ever is -- but if it were, by dichotomizing it to a success/failure, you are throwing away 36 percent of the information; 36 percent.

That means you have to increase your sample size 57 percent over not using the continuous scale. That is just a little math calculation. I could do it, so I did it, and that is the result.

I have heard talk about entry criteria and exclusions. Again, I have to say I am a statistician. I just want to see things -- I think statisticians are often accused of wanting to do things on, as we used to say, we want everybody to be the pure bred white rat; excuse me for using that analogy.

Actually, that is not what we want. We want everything to work. Now, where are the devices going to be used? They are going to be used on probably a fairly broad population.

I would argue, entry criteria for a trial should be a person who may benefit from the device. That is my entry criteria, a person who could benefit, and should mimic practical use of the future device as much as possible. Otherwise, you are going to have questions when it is used beyond the scope of the entry.

I have had doctors come to me and say, you know, this study said you had to have this test done and this done and this done. Gee, I don't have time to do all those and I have got to treat the patient. What do I do? Is this the right treatment.

The patient population treated in the study was just too small, too narrow to be generally applicable. So, I believe in entry criteria being broad.

The sample size and design should be appropriate to the goal of the study, whether it is equivalence or superiority, and you have got to state -- I guess you should state the goal of the study before you start; right? Isn't that what you should do?

Sample size and design should be appropriate to that. Let me say that sample size and design is relatively

easy for randomized trials and is more problematic for non-randomized trials.

Some talk about centers and pooling across centers, and pooling across different populations that may enter the study.

I think, given what I said that the population should be broad, what do I do about that question. What I do about that question, I think you have got to model whether or not these populations can be poolable.

I think there are statistical methods now that allow you to do that modeling, to do it based on the data that you get from the study.

I think the question is not to pool or not pool. In fact, the question is, how much should you put the information together and how much should it be considered separately, and it is a different point of view.

I do expect centers not to be identical. I do expect there to be variation in centers. I think there should be.

What if all the centers you put in the study were identical? Then what happens when you want to use that device in a center that is a little different. Again, I think that has to do with generalizability of the study.

In addition to justification for sample size, I think it is absolutely critical that there be a clear

statistical analysis planned in the IDE up front.

If you don't have a clear statistical analysis planned, a clear -- I don't mean, we are going to use chi squared; that is my plan. That is not enough.

You have got to have a clear plan for how you are going to handle the data, how you are going to go forward.

Let me say, that is real easy for randomized trials. Guess what? For non-randomized trials, that is much more problematic. How you are going to pool that historical or that concurrent control data, that is a big question. It can be done, but it deserves a lot of prior thought.

Last comment. When you collect data over time, you should analyze data over time. Longitudinal data analysis is an important aspect of many of these scales, pain, even fusion function. They are collected over time. You should look at the change over time and analyze that change over time. That is enough.

DR. BOYAN: Thank you. Dr. Nelson?

DR. NELSON: I only have one point. We have somewhat skirted around this, but I think we should bring this up a little more obviously.

We are talking generally about spinal assemblies. Most of the comments people had related just to fusion products. I think we need to segregate these out.

I think we are giving the FDA a lot of good guidance about fusion products. We are giving them almost no guidance about, say, artificial discs, et cetera, and we just have to recognize that we are doing that.

For instance, we are talking about 12 month fusion follow up, et cetera. We are not talking about discs. So, we ought to separate those two out. Other than that, I have no comments.

DR. BOYAN: Dr. Ducker, I think you are -- did you have something?

DR. DUCKER: I will wait until we come around again. The only point, I will send to Demian some of this material which does the measurements and what you can expect from 2,000 low back surgeries or 500 neck surgeries.

DR. BOYAN: Thank you. Dr. Holeman?

DR. HOLEMAN: My comments really relate to the assessment of pain and keeping pain as an end point, I will say relative to using fusion, as an end point.

I don't believe that when a patient comes to a physician, the patient comes to the physician requesting a fusion.

I think they come with symptoms indicative of pain or severe pain, and the idea would be to relieve the pain.

So, I see maybe fusion being an end point as to the effectiveness of the device, but I also see pain as

being the end point for patient effectiveness.

MS. MAHER: Hi, this is Sally Maher. From an industry standpoint, what we are really looking for is a guidance document that will be helpful but also will be flexible, so that when we come in with different types of devices, we are not all getting tied into the exact same mold.

Quite honestly, all of them are different; all the needs are different and all the indications are different. We need to have some guidance, and that is very helpful, but a lot of flexibility to come with it.

DR. BOYAN: Dr. Witten, is there any comment you want to make?

DR. WITTEN: Not yet, thanks.

DR. BOYAN: Okay, Dr. Aboulafia?

DR. ABOULAFIA: Many of the issues have already been addressed and I think there is already a lot of common ground between panel members and industry.

A lot has been discussed about two issues; whether pain is variable that needs to be controlled or not, and then what is the definition of fusion.

It has even been mentioned by someone in this room already today to use bone scan. I think we could for the most part agree that bone scan is almost universally not helpful, so I would exclude that from the discussion.

One of the questions I would have is, we have talked about thin section CT and reconstruction within section CT.

I don't know if anyone has an idea of the sensitivity or specificity of thin section CT, and maybe even more appropriately, positive predictive value and negative predictive value.

At least industry suggested that we use that as the prime criteria of whether the implant is doing its intended goal with the exclusion of pain and other variables.

Then we have used a model, or it has been suggested that we use a model that we really don't know what the sensitivity and specificity of the study itself is.

I would also say that flexion extension views shouldn't be left out. Flexion extension views are easy, they are reproducible.

While it doesn't tell you that you do have a fusion, it will frequently tell you that you don't have a fusion. So, it may have a very good negative predictive value.

Its positive predictive value may not be very helpful. I think in the absence of being able to say with certainty, even though the gold standard may be thin section CT, I think flexion extension views are easy, they are

simple, they are reproducible.

The other thing with thin section CT is we don't know what the reproducibility in reading it is. Does one radiologist like David Hackney see a thin section CT and be reasonably convinced that there is a fusion? Another radiologist may look at the same thin section CT and think that there may not be.

We have seen convincing CTs that are indisputable that Dr. Zdeblick showed, that show indisputable fusion mass, but there are gray zones in this area. Not every time is it easily predicted.

The other thing about pain as being an end point, I would echo Dr. Holeman's comments, but also pain not only in terms of whether it relieved the patient's symptoms, because you are right, as suggested by Drs. Kahanovitz and Zdeblick, that that measures the surgery and not the implant.

I would say that is true if you think of it in just half the sense. Maybe the implant itself causes pain.

So, if we are looking at things that the implant, or just looking at the function of the implant, then I think you could argue the other way, that pain should still stay in that equation. I don't know if that made sense, but I hope it did.

One year follow up, I think Dr. Hanley already

addressed. I think it is probably reasonable. I think industry is actually taking a bit of a risk.

There are patients who may not show a fusion at one year. Clearly, the numbers are not going to get better for them. It is only going to get worse for them.

I think if they are willing to take that calculated risk, I think it is certainly reasonable.

There was some discussion about whether a pilot study needed to be done or not. I think there are already a huge number of similar devices which have been implanted. We have some of that information already, and with some of the information that has already been done, you could say that a pilot study has already been done and that certainly isn't necessary.

The other thing that was addressed by Dr. Larntz was inclusion criteria. I agree; I would hate to see the inclusion criteria be so rigid.

I think the reality is that there are many obese patients who undergo this procedure. Why would we want to exclude some of the largest group of patients who this procedure is intended for.

Similarly, I would say if industry wanted to include smoking patients with the understanding that smoking patients may decrease the number successes, as we are defining success as fusion, then they should be included in

the study.

As Dr. Larntz said, he wants to include things as much as possible. I would agree with that.

If you find out, as you are doing the study, that the incidence of non-unions in smoking patients is much higher or unacceptably high, then fine. That is what longitudinal evaluation of data is intended for. Also, that data can be stratified later on. I would want to get more patients on.

Then the final issue that has been brought up once. I agree, metastatic patients are clearly a very different group.

I think you are looking at 100 percent, two ends of a coin. In patients with metastatic disease, assuming patients who have a limited life expectancy of, let's say, less than a year, you are not necessarily looking to obtain a fusion.

Currently in patients who have metastatic disease, we are frequently using polymethylmethacrolate as a huge spacer with implants, whether they be stemic ends or anything else.

Fusion is not a measure of success. There is no intention in the world whatsoever in trying to obtain a fusion. So, it is a different group of patients.

What you are looking for is pain relief, mobility

and neurological status. I think those are just, again, to mention very separate issues that I think are easy to control as well.

DR. LAURENCIN: Just a few points. Many of the things have already been said. First, I think that the panel in general is very sympathetic to this sort of document.

I think everyone on the panel has been involved in studies with the FDA in which we have tried to design a study and then find that there are differences and changes that are made.

So, a guidance document is something that is very, very welcome and something that we try to rely upon, that I try to rely upon in my area of research interest.

As such, we would like to have a document that is also flexible enough, that gives a range of different possibilities in terms of being able to carry out a study.

The second point is, I shudder when I hear that there are thoughts in terms of a spinal fusion operation, that fusion would be the predominant end point for the operation instead of pain.

We have to all remember that the reason why we are all here as doctors is actually to relieve pain. That is the whole reason why we actually place a patient through a procedure for spinal fusion, in most cases.

I think that is of paramount importance and I think there should be really a paramount emphasis on that.

I think it is very difficult to explain to a patient that they have had an operation done and it has been very, very successful. I know you have a lot of pain, but it was very successful; look at the X-rays. I think it is very, very important to emphasize.

The third is the whole question about time needed to determine outcomes. We had a meeting last year in which a large mound of data was presented to us in terms of papers and outcome studies. There was a debate between 12 months or two years in terms of looking at overall outcomes.

I think the conclusion of the panel -- I may be corrected -- was that 24 months was the time point for follow up that was needed for the range of spine operations that we see.

That may change, but just in terms of what our consensus was from our meeting and the direct questions given to us, I believe that two years was given.

Last, in terms of randomized studies, I believe that prospective randomized studies are ideal. I think, are they difficult to do; yes. Are they possible to do; yes.

We have set a bar. The bar has been set for a number of devices, including spinal devices, in order to pursue prospective randomized studies.

We have seen companies come to this panel with prospective randomized studies involving spinal implants, and these products have actually been approved for use by the FDA.

I do think it is a -- I don't think it is an unreasonable goal to pursue and there may be deviations in that goal.

We have also seen it happen where companies have started and worked very earnest. Just as Dr. Larntz said, they may actually stray from that, and actually sometimes it is even more work for them if they do stray from that.

At least I believe that we should continue and have that bar at that level that we set for other devices, and for the spinal devices with prospective randomized studies.

DR. SKINNER: Obviously, much has been said already. I would just like to make a couple comments. First of all, regarding the 24-month, two-year study period.

I think the comments by the private doctors, the academic doctors and the industry have been very cogent on that topic.

I think that the best thing to do is to schedule a two-year study with the possibility, with the FDA approval, of interim analysis. By interim analysis, not that we are going to collect patients until we have a statistical

difference.

I think that scheduled interim analysis would be the appropriate way to go. You get the best of both possible worlds.

If, for some reason, you don't have statistical equivalence at six months for cervicals and one year for lumbar, you still have an opportunity to carry that study out further and show statistical significance.

The other topic of interest is the pilot study. I think the pilot study is a very important item and shouldn't be disregarded.

The pilot study gives you a chance to eliminate failures from your real study. Anything that is significantly new that the FDA recommends a pilot study on usually is going to have a significant learning curve on, and it gives you a chance to improve your statistics later on, and it gives you a chance to work out your standard deviations so that you can more adequately plan your real studies.

I think those are important things to keep in mind. It doesn't mean, I think, that every study should have a pilot study involved.

DR. CHENG: I just have four comments and then a question. The first comment was that I would like to impress upon the FDA that I would try to shoot for the

middle ground in terms of the usage of these guideline documents and construction of it, because of all the comments that were already made that concern how specific the document is.

It does need to be specific enough for it to be useful. Otherwise, it is not of use and doesn't set a level playing field for everyone.

There are guidelines only and they can change. So, I don't really see that much harm in at least specifying some concrete or some specificity to the document.

That leads me to the next comment. We discussed at length last December the 12 or 24 month guideline, or outcome length follow up time.

It is interesting to me that a number of representatives of industry argued for the 24-month time period at that time and now argue for a 12-month time point.

I would maintain that our standard journal in the field does have a policy of a 24-month time point unless it can be shown otherwise for a procedure.

The FDA should at least maintain the same stringent standards as our journals.

The second or the next comment deals with the end point of fusion and pain. My take would be a little bit different than Dr. Laurencin's.

I think the device is intended to fuse the spine,

much as a suture is intended to hold something together. We don't judge a suture in terms of whether it relieves pain, although it is a portion of the procedure.

The fourth would deal with randomized trials. I am involved in running a randomized trial myself. The two arms are very similar and I have not had a lot of difficulty in enrolling the patients.

Now, maybe they are so similar that we are not going to find any difference. There are times that a randomized trial could be run. I think it is a gold standard and you should shoot for that.

The FDA can specify that the data from a randomized prospective trial is more valuable and cleaner than one from a concurrent controlled type of trial.

That is not to say that those trials shouldn't be done and some people mentioned there are cases where that is the only type of trial that can be done.

The last question I have, it wasn't clear to me whether Dr. Kahanovitz was speaking on behalf of himself or the Spine Society.

Unfortunately, he has left, but is that is his comment or if that is a policy statement by the board.

DR. BOYAN: Is there anybody who can respond to whether that is an official policy statement by the board?

I don't normally have anything to say, but I am

going to take one opportunity here to speak, because I represent the loyal biology group.

This is a hardware document, and I think it is a really wonderful hardware document. The new products are software, and we need to leave some flexibility in the document for new information that is going to come about from the biologically oriented products.

We don't really know what all the outcomes are that will be associated with them and in what time frame they will manifest.

While I agree with the comments from industry that given the current state of the art, the hardware, that certainly if it is going to fuse, it fuses within a reasonable period of time.

There is a lot of experience now and an expectation could be made and probably relied upon that, over a one-year period for a lumbar and six months for cervical, there is going to be data that is going to be useful and would help FDA make a rational decision about that device.

I would hate to see something written here to be an absolute statement of any kind about length of time. As the new products come along, they will have both pharmacological and maybe biological consequences that will occur later than that.

There needs to be room to give FDA the option of assessing it adequately. Over to you, Dr. Clauw.

DR. CLAUW: Most of what I want to just say has already been said. I would like to weigh in on the issue of outcome measures and the relative importance of pain as an outcome measure.

I would like to reiterate what a couple of people said. I was cringing as surgeon after surgeon was getting up and saying that pain was not an important outcome measure.

I was heartened by a number of the people on the committee who have come forth and said that it is a very important outcome measure.

I would argue that it is the opposite. I would argue that fusion is largely irrelevant in assessing whether a device is efficacious or not.

Again, patients don't come to us and say that their back is unstable and that they need their back stabilized. They come to us with pain or with dysfunction.

A comparable analogy is me as a rheumatologist, taking care of a patient with rheumatoid arthritis, giving them an anti-inflammatory drug and having the person come in no better and me telling them, well, your sedimentation rate is better or some measure of inflammation is better, so you must be better.

Again, it is what the person presents with. Efficacy is defined as an improvement in the patient's condition and not by the radiographic improvement or stability that a device can offer.

Again, let's get back to what we are putting the device in for. The device is being put in to improve the patient's pain and improve the patient's function.

Having said this, I think that there are some slight modifications that could be made to make these outcome measures perhaps less onerous.

I think that the reason that a lot of people in industry and some of the orthopedic surgeons take issue with this is due to the fact that, as they are laid out right now in the guidance document, they probably are too stringent.

For example, in rheumatoid arthritis and osteoarthritis, where there has been a lot of work trying to determine what is a clinically significant improvement, what is generally found is, for example, the pain function and some other measure, they will require that two of the three improve, rather than all three improve.

You could envision that a similar type of thing could be done with a device such that if pain, function and stability or fusion were the outcome measures, that if two of those three improved, that that would be judged a clinical success, rather than requiring that all three

improve for that to be judged a clinical success.

Again, let's not get too caught up in this issue of pain and improvement in pain. We are not really saying that a device in every person has to improve pain.

All we are doing is that when we compare it to a comparison group or a control group, that it is equivalent to, or superior to, depending upon the study design, to that comparison group.

We know better than to think that in every individual the device is going to improve pain. On the average, and using statistical methods, we have to show either an equivalence or a superiority in that regard.

DR. BOYAN: Now, for the radiologist.

DR. HACKNEY: I am going to start by talking about the non-radiologic issues, and then go on to what I know I am talking about.

So, what have the comments been about the double blinded study, the impossibility of blinding the surgery. You have to have the surgeon do the evaluation. You have to have someone who is blind to what fusion device was employed do the evaluation and subsequent clinical evaluation of the patient so that you can maintain that objectivity.

Secondly, I think that the only circumstance in which fusion is the only outcome criteria is when you are dealing with a patient with an initially unstable spine,

such as a fracture, where that really is the goal, is to make that spine stable. In that case, fusion could be the only outcome criteria.

You still want to know whether it made the patient clinically worse, but that was the goal. Otherwise, I think you have to keep pain as an evaluation criteria. As has been said over and over again, that was the purpose of doing it.

If you do keep pain as an evaluation criteria, then that becomes a rationale for a longer post-op evaluation period.

It may be true that you can evaluate fusion quite quickly in the vast majority of people who are going to fuse. That doesn't mean that their full clinical outcome as a result of the surgery has been determined that quickly.

I certainly sympathize with manufacturers who negotiate a study design with FDA, only to discover when they come to a panel meeting that the panel doesn't like that design.

I have seen that happen and, I agree, it is profoundly unfair. I don't know whether this is a matter of FDA policy and not something that would be in this document, but there should be a way to commit the FDA and the panel to accepting the results generated from a study, if they have already accepted the study design. They should not be able

to retrospectively rewrite the study design after the study is done.

I agree that this will become a guidance document and that the FDA should be able to negotiate the appropriate deviations from this guidance for a particular study.

I think there is nothing in here that could be interpreted as saying that all studies have to be done in exactly this manner.

The FDA should really require, for example, for clinical outcome measures, that the measures that are used are defined beforehand, and that the rationale for using both the instrument and the degree of change are defined and justified. I don't think it is necessary to say what those are in this document.

As to radiologic issues, the only way you could prove the accuracy of bridging trabecular bone on CT is either to collect a group of human cadavers who had been fused during life and inspect their spines, or do a large animal series of studies.

Small animals are very much easier to image for these purposes, but you have to design a set of fusion devices that can fit small animals. Then you would never know whether they really work the same way.

You would have to find large weight-bearing animals who walk upright. I think that the perception that

bridging bone across a space indicates fusion is based on studies of other joints, and it is based ultimately on the clinical outcome of people who appear to be stably fused by radiographic criteria.

I think we are back at the same point. Ultimately you want to know whether this does the patient some good.

I agree with most of the comments that were made earlier about expanding some of the radiographic studies that one could use in evaluation.

Tomography is a wonderful technique but no one does it anymore. The machines are large and expensive. They break down a lot. Obviously, most radiology departments have retired them. This is about the only time that anybody regrets that, so I don't think they are coming back.

DR. BOYAN: Are there any other general comments by the panel that they would like to make?

DR. NELSON: I would like echo I think it was Dr. Cheng's comment, that you don't judge the effectiveness of viacralsuture by whether or not the patient's back pain goes away after the back surgery.

Basically, the viacralsuture just has to hold until the wound closes. The way you test the suture, you look at the wound closure.

I agree with Dr. Zdeblick. I think if the device

is only intended to create fusion, then the fusion should be the criteria and the effectiveness of the pain relief relates to whether or not you picked the right type of surgery for this particular type of problem.

I think we have to segregate out all those other devices which aren't doing that, like artificial discs. For fusion, I don't think pain really is going to be a relevant criteria.

I think you need to collect it maybe as a secondary criteria for looking at other things, but not for does this create fusion or not.

DR. SKINNER: That is fine, David. If I give you a bunch of X-rays on patients I have done total hips on, and show you the hip films on them and you examine them and they all look great to you, and then I happen to mention that I have lengthened all their legs by two centimeters and they have sciatic nerve palsies, those patients are going to have a problem that they are not going to be very happy about as a direct result of the surgery I did.

It is a complication of the prosthesis I used, and that is why you have to monitor the pain. It is potentially a direct result of the procedure, not necessarily an associated result of the procedure.

DR. NELSON: Dr. Skinner, are you willing to accept having it as a secondary end point rather than a

primary end point?

DR. SKINNER: Sure.

DR. BOYAN: What I would like to do now is to address the questions, just go through them very quickly, and just to make life simple, we will always start with Dr. Clauw.

You don't have to comment. If you feel like you have already covered this issue or that it has been covered to death, don't feel obligated to make a comment.

As you look at the question, if there is something you would like to add as we go around the room, please add it now. We are just going to march our way through the questions.

What we really need is, I think, Dr. Panitch or Mr. Melkerson, who is going to do the computer stuff.

The first question is, the spinal clinical assessments of pain, function and neurological status and performed pre and post-operatively.

They would like any information we could provide to them on the instruments to be used, entry criteria, success criteria and cervical versus lumbar differences in these criteria. Dr. Clauw.

DR. CLAUW: The types of instruments that are noted in the document are all good instruments and, as other people have noted, there are other good instruments. So,

again, I think it should be made clear that this is not meant to be all inclusive.

With respect to entry criteria, I think that a big reason for entry and exclusion criteria in studies are to ensure that you are getting a relatively homogeneous group of patients that will benefit from whatever you are doing.

Again, I am not buying the suture analogy at all. I think that entry and exclusion criteria should be used in a study to ensure that what you are doing is getting patients who would benefit from a fusion procedure, and that we can separate out the device that is meant to fuse something from the indication for which it is being used.

I do agree that there are differences between cervical and lumbar regions, certainly with respect to the validated outcome measures, but also in the cervical region, fusion seems to occur more rapidly, and perhaps the study length would need to be more.

DR. BOYAN: Thank you. Before we go to you, Dr. Hackney, can I enter something into the record? We were asked whether or not the comments of Dr. Kahanovitz were his own personal comments or represented the North American Spine Society.

The letter that he sent, which actually is the written version of what he read to us, is on the North American Spine Society stationary. I think we can assume

that it reflects the position, at least, of the management of that society.

DR. LAURENCIN: I am not sure, can you really do that. I mean, it is dated two days ago and it has a cc to the board of directors. I think we should have that clarified.

DR. BOYAN: Point well taken. I think for the purposes of FDA, that you might want to clarify that this is their position. Okay.

DR. HACKNEY: I addressed this already on question one. I think that it is fine to include assessment instruments as long as it is clear that it is not intended to be an all-inclusive list, that manufacturers can substitute others, provided they have adequate justification for doing so.

DR. WITTEN: Dr. Boyan, I was going to wait until the end of this round of responses to comment on that, but since it has come up several times, I would just like to clarify that a guidance document is meant to be just that, only guidance for industry, to give them just some framework in order to present a study.

There is nothing in the guidance document that is meant to be a requirement. When examples are provided, they are provided purely in order to be helpful.

We certainly would look at any other assessment

tools that a sponsor provided, and in fact, we would be interested in your comments about additional assessment tools, not for the purposes of adding to the requirements of this document, but merely to shed some additional light on what might be a menu of possible options that would be good for industry to take a look at.

DR. BOYAN: Thank you very much, Dr. Witten.

DR. HANLEY: I would just like to make the comment that I agree with Dr. Kahanovitz, I believe, is the one who said that some of these measurement instruments have been developed by consensus by large groups of doctors who do this stuff.

If you have a validated tool that the doctors have found successful, that they are more likely to use it. I think we should keep that in mind and try to emphasize that rather than use some obscure thing that we may or may not buy into.

DR. LARNTZ: No further comment. I made a comment about entry criteria. I stand by that comment.

DR. NELSON: No comment.

DR. HOLEMAN: No comment.

MS. MAHER: My only comment is a comment on Dr. Witten's comment. From an industry standpoint, while guidance documents, we all understand, are truly supposed to be guidance and supposed to only give us frameworks to work

in, in fact they frequently become much more than that, if for no other reason than because it is easier for somebody to say, no, you are supposed to do it this way.

The broader and the more general the document can be written to make sure that everybody understands and feels that there is flexibility in it, the easier it will be for it to be a living document that can be useful for much longer than this year and next year with the technologies we currently know.

DR. ABOULAFIA: I think Dr. Clauw has already gone through most of the things. Instrument to be used, we have already addressed, and I think is appropriately addressed in the document.

Entry criteria, I want to be more inclusive than exclusive, and agree with Dr. Larntz that the more you include, even though it dilutes the population to some extent and it requires more statistical analysis, I think to exclude obese patients, as I mentioned before, or even smokers probably does a disservice to industry.

Success criteria, again, I am just going to bring up the point about pain again, because it is something that keeps going back and forth.

To use the suture analogy, again, while it is intended to hold the wound together and maybe two different sutures do that equally effectively, if one promotes

infection and the other one does not, then that would be another thing to look at.

I think pain, again, is an important criteria to be included. I could probably go along with Dr. Skinner and put it in the back seat rather than the front seat of the car, but I think it needs to be in the car.

Then, again, just a sentence that I would still include flexion extension views, in spite of whatever CT -- with CT reconstructions -- thin section CT and CT reconstructions do.

I think it is simple, it is easy, it is reproducible. It has limited inner observer variability and, for no other reason than that, would include it.

DR. LAURENCIN: Nothing to add. Again, just emphasizing again, I think that pain should be the major criteria.

If you had a device that somehow in some way evoked an extremely strong proliferative fibrous response, and you had a fibrous union but it was a very dense fibrous union, and patients, for some reason, came out and had no pain whatsoever afterwards, you would actually call that a successful implant. It is a different way of doing it, but it is a successful implant.

Again, my feeling is, looking at what the patient is coming in, what the complaint is and treating that

complaint is what we should be doing.

DR. ABOULAFIA: I forgot one other point. The topic about follow up period, the 24 month follow up period was, and still is for one of our peer reviewed journals, is for reconstructive procedures specifically.

They publish articles with less than one year follow up on non-reconstructive procedures. When you look at closed intermedullary rodding of open tibia fractures, the follow up period was less than two years, where the goal is to obtain a union without an infection.

It is also not the only peer reviewed journal in existence, even though some people may want you to believe that.

There are other peer reviewed scientific journals with very good reviewers and editorial boards who accept less than two year follow up.

If the goal of this is to obtain fusion and industry can demonstrate that with less than two year follow up and, I would argue, pain relief with less than two year follow up, then I think they have met that standard.

DR. YASZEMSKI: Two short comments. One, it appears to me we are past Dr. Larntz again and he can perhaps comment on this next time around.

I recall that there is a design called a randomized surgeon design, where it is a prospective

randomized design and each surgeon who enters gets to recommend and do his or her most preferred treatment, and the patients are randomized by surgeon.

Of course, it requires that these surgeons are all at the same institution and the patients have a way of getting from one to another after being identified. Perhaps a little further comment whether that is reasonable from our statistical consultant.

Second, we have all been weighing in on the pain and fusion issue. I will agree that it is very important to consider pain.

I will say that my feeling is that it should be a secondary thing, and to give consideration to fusion primarily, and to follow pain, just to be certain that we are not missing anything negative or detrimental for the patient that comes about from the procedure.

DR. SKINNER: I basically agree with Dr. Yaszemski regarding the back seat for the pain. I think that we have to recognize that back pain patients are a different breed. There are problems in pain in those patients to some extent.

I think it is important, should be in the car, but it should be in the back seat.

Regarding the instruments that should be used, I think we should point out that we don't have to have all the instruments used.

Let me just clarify what I said. I think that fusion is an outcome of the device and pain is an outcome of the operation. It is important, but it is of secondary importance.

While fusion is very, very difficult to measure, as we just talked about, pain is even harder to measure in the subjective.

I am not saying that it is not important. It is very important and the other comments deal with really complications. I mean, they are an outcome of the operation but those are complications as well.

DR. WITTEN: I appreciate all the comments. There are a couple of things that I would like some additional input on. You don't have to go around the room. You can ask for volunteers.

DR. BOYAN: You mean we don't have to do the next eight questions?

DR. WITTEN: No, you do have to do the next eight questions. Before you do the next eight questions, relating to this question, I have a two-part question.

One is, although I recognize the concern about recommending any specific instrument, because of the fear that FDA will then require every sponsor to use that instrument in every study, still, I think we would be interested in knowing if there are any specific instruments

looking at the effect of pain on function, that any of the panel would care to offer up as suggestions for sponsors to consider.

In particular, one of the reviewers from the panel mentioned the NASS and Modems instruments. I would be interested to know if there is any information that suggests that those are responsive to clinical change; that is, following a surgery, that you could expect to see changes in what those instruments measure. That is the first part of my question. It is a two-part question.

The second one is just related to that. As someone on the panel mentioned already, we may need to look at success/failure for fusion versus non-fusion devices separately.

So, there has been a lot of discussion on -- in this question, related to fusion devices. We are interested in success related to non-fusion implants also.

This is going to come up in question number five. I just want to mention, when we talk about success instruments, I would be interested in hearing any comments as they relate to these other types of assemblies.

DR. BOYAN: You have heard the question. Do I have any volunteers from the panel to address it?

DR. DUCKER: Daniel will give you a name at NIH, by the name of Rick Gaisely(?) that he just gave to me, who

has developed pain scales and things.

I will send to you the NIH-sponsored grant with 2,000 patients in the lumbar area with their three to four year follow up and the 500 patients that are in the cervical spine research with their one-year follow up.

All this is going to be published in Spine or various journals this year. These are instruments that are designed to focus, and they deal with pain, function, social and actually they even deal with your continuing medical needs.

In other words, one of the measures is how many times do you still go back to the doctor for your complaints.

In response to Dr. Cheng, as a follow up of these studies, clearly I know there are seven orthopedists here, and Daniel in rheumatology and myself are sort of the odd man out.

Other journals do not require that kind of follow up. For neurologic journals, basically it is one year. For infection it is six months. For the New England Journal, I have reviewed spinal cord injury, which is one year. So, a lot of things.

I know you are married to one journal, but some of us are married to another one. So, you have to measure each one separately. I would look at it in the broad spectrum.

In answer to your question, we will mail to you or your panel these other instruments which have been thoroughly documented by a bunch of smart people that I have just taken it from them.

DR. CLAUW: The sections on outcome measures in here are very well written. They really represent sort of the state of knowledge about outcome measures. The Oswestry and the Roland Morris are by far the best validated of the ones for low back, and the ones that are listed for the C spine are all sort of relatively equal.

I am not aware that there have been good validation studies with the measures that have been developed by the North American Spine Society.

If there are, then those would likewise be reasonable to use. These really would be, either by most psychometricians, people who are in the business of developing outcome measures and looking at how valid and reliable they are, as being sort of the gold standard.

Likewise, the SF36, they have run a couple of studies in the last couple of years. In the group of people that have musculoskeletal disorders, the SF36 is the best generic measure of health status.

There are other measures like the Euroqual and things like that. When you are looking at musculoskeletal disorders in general, this has been specifically looked at

in patients with low back pain.

It is the best generic health status measure. So, again, these sections are very well written. I think that all of us are just saying, don't try to mandate that these are the ones to use. There are other ones that might be equally good.

DR. BOYAN: There was one comment. Dr. Persenaire, did you want to add something?

MS. MAHER: Everybody has been talking about all the magazines that require the two-year follow up. Spine Magazine actually says that they recommend a two-year follow up. They don't require it.

In fact, there is an article in the August one, which only had a four-month follow up. I think to keep saying the two-year follow up is something that magazines are requiring is a little bit of a misstatement. I just wanted to clarify that.

DR. HANLEY: That is a scientific journal, not a magazine.

MS. MAHER: Excuse me; point taken.

DR. HANLEY: Like Esquire.

MS. MAHER: It is my lawyer background, not my science background.

DR. BOYAN: You can't hold them down. I think what we are trying to say, though, is that good science is

good science and that ought to dictate the study.

DR. PERSENAIRE: The discussion about the different instruments to be used in designing studies, every time you do it each new year somebody else has done a study and proven that he has a very valid instrument. I think that will continue for some time to come.

To make data truly comparable, it would be helpful if the panel would say, yes, we believe the SF36 is a good, overall quality of health measurement, yes, the visual analog scale is at this time, at least, one of the better ways to have the patient indicate his level of pain, so that longitudinally we can follow patients and compare studies.

DR. CLAUW: Again, the SF36 is very well validated. You can never go wrong by using the SF36. The visual analog scale is not a good way of measuring pain. A lot of people still use it.

The problem is, there is no unanimity of what to replace it with. The McGill short form, again, would probably be the best generic measure of pain.

That, again, is not well standardized for specific areas of the body. One of the problems with measuring pain is that you really want to try to capture the pain in the area of the body where you are doing the surgery and not global pain, especially since many of these patients may have pain in more than one area of the body.

Again, it is not likely that if you use these outcome measures that anyone is going to be critical. These have all been well validated.

You are a lot more likely to be on thin ice if you venture out onto your own and use something that someone has developed, and perhaps not nearly as well validated.

DR. BOYAN: One last comment?

DR. KITCHEL: I would just like to ask a question, if I could. I believe I heard Dr. Laurencin say in the discussion a few moments ago that the panel had now been presented a number of prospectively randomized controlled studies on spinal implants which had led to their approval.

I am not aware of those. My impression was that there, indeed, has not been a single prospectively randomized controlled study of a spinal implant that has gone through this panel that has led to approval. I wonder if he could clarify that.

DR. BOYAN: Let me handle that. That is sort of a chairman issue, I think. I think that your comments right now, first of all, we are not always aware of what leads to approval or not. We only advise the FDA.

Secondly, outside of this field, other fields do come in with prospective randomized clinical trials, and I think that may have been what was referred to. Okay, so let's now move to question number two.

Radiographic assessments. Should there be plane film, CT, MRI, myelography, discography. What are the criteria which constitute fusion and what constitutes validation of a method.

Since this is a radiographic question, I think it is fitting that Dr. Hackney start the discussion.

DR. HACKNEY: I think that defining the precision and reproducibility of the radiologic interpretation is part of the study design.

There is no technique, as I mentioned, that has been validated against the group of volunteers that has been willing to be sacrificed at the end of two years.

You are basing that on your belief of what the radiographic findings would imply, and what they have implied in other patients who have ended up apparently fused and got better.

The precision you can certainly define in the scope of a study, and in the study you will find out whether apparent fusion by radiographic criteria correlates with anything else that you care about.

I think that a guidance document should probably say something along the lines that the manufacturer should select and justify the imaging criteria that will be used.

Right now most people would certainly accept bridging osteoplates across an interspace on a

reconstructive CT scan.

Everybody would also recognize that it might be difficult to see that, even if it is present. I think many people would wonder whether you can reliably distinguish that in most cases, particularly in the sorts of devices that include bones packed into a fusion cage.

You can identify both whether they bridge from the inside of the cage across the interspace, and that may not be obvious. That is why you have to validate whatever else you have such as a relationship with the patient's outcome.

Now, what specific techniques other than that? The traditional ones would be plane films and flexion and extension views.

People have commented about the potential limitations of those. I would agree with them. Probably the document should say that the list of acceptable imaging studies for assessing fusion generally should be drawn from a short list of thin section CT format, plane film and flexion and extension plane films.

Many of these others are used for other purposes. I don't think that myelography, discography or MR are particularly useful for assessing fusion. They are used for many other indications, but not for that.

I think the main issue here, again, is that when the manufacturer generates the study design, they have to

address the issue of how reliable their radiologic criteria are, provide a background that suggests they should be reliable, and provide a way of testing whether they are at least reproducible, and whether they correlate with something else that we care about.

DR. BOYAN: Thank you. Rather than going all the way around the table, why don't we now open it up to anybody on the panel who would like to make an additional comment, in addition to what Dr. Hackney has said, or who maybe takes umbrage with something that he said and would like to offer an alternative view.

DR. LARNTZ: The only comment I would have is that, if possible, these films should be read by an independent assessor.

They should be read and decisions made about fusion, either in a core lab or outside, a person not associated with the study.

DR. BOYAN: Would it be fair to say, Dr. Aboulafia, that you want to make sure that the flexion and extension radiographs are made?

DR. ABOULAFIA: Dr. Hackney mentioned that. Also, you may want more than one radiologist, so two or three, and then reproducibility within the group.

So, you would compare the radiologists' interpretation among the three of them. Then you would give

them the same radiographs three months later and have them read the same X-rays three months later, and see if the same radiologists agree with themselves.

A lot of that comes from studies that have been done in upper extremity for wrist fractures, and looking at displacement and things like that.

DR. HACKNEY: That is appropriate quality control and a good idea.

DR. CHENG: May I make one comment?

DR. BOYAN: Please.

DR. CHENG: Just a suggestion from my experience. By packing holes with bone by allograft or olograft, you can get an X-ray afterwards that shows that the area is very well filled in with bone, but it is not healed, and it will go away.

I think you mentioned one sentence in regard to that. I think watching studies over time to assure that there is the formation of mature, remodeled bone, until you are convinced of that, is very important.

It may not just be one test or one flexion extension film, but over time, certainly that would increase your level of confidence that you have a mature fusion.

DR. BOYAN: My I comment on that? I think that raises an issue that is very important from a biological point of view.

Some of the newer materials may, in fact, give the impression that there has been a solid fusion. In fact, after they are modeled or resorbed, the outcome may not be as wonderful as it first appeared.

I think that does need to be taken into consideration in the study design. Dr. Hanley?

DR. HANLEY: Just to comment on entry into the study, we have been talking about outcome assessments here with radiology.

On the similar vein, I think for each diagnostic category, for patient entry into a study, they should define whatever radiographic or imaging criteria will be utilized to place a patient in the suitable category.

I think that is in the document already, but I do want to emphasize the entry imaging studies, in addition to the exiting ones.

DR. BOYAN: Any other comments? Ms. Maher?

MS. MAHER: Just one comment regarding the radiographic assessments. I believe that the IDE that goes in should clearly define what the sponsor believes the best method of determining fusion is, and should be justified in the IDE.

This guidance document shouldn't necessarily be prescriptive as to how many extra people need to read the X-ray, et cetera.

That really should be the sponsor's call as they submit the IDE. It makes me very nervous to think about adding a tremendous amount of extra cost to a study that may not be necessary. I think it is up to the sponsor and depends on the device itself.

DR. BOYAN: FDA, have we adequately addressed the question of myelography and discography?

DR. WITTEN: Yes. I wasn't going to ask about myelography or discography, but I was going to ask an additional question about this question.

That relates to the interpretation of flexion extension films, and at what point, seeing no motion on those films, can allow you to interpret that fusion has occurred, in particular since some of the devices may provide stabilization immediately.

DR. ABOULAFIA: None. We addressed that a little bit when I said that it doesn't tell you that you do have a fusion.

If there is motion, it tells you that you don't have a fusion. So, it has a very good negative predictive value, not a positive predictive value.

Then, in terms of just making Ms. Maher nervous, this is a guidance document and we are being asked to give guidance.

My guidance is that you should have more than one

radiologist read the X-rays. Our statistician, who I respect, agreed with it.

All it is, it is intended -- everything we have said is intended as guidance. I think if someone wants to come with a proposal for an IDE that they are going to have one radiologist read the X-rays once and only once, that is fine.

We are guiding them in a direction now to suggest that that may not be in their best interests.

DR. BOYAN: Okay, have we adequately addressed the concerns of FDA with this question?

DR. WITTEN: Yes, thank you.

DR. BOYAN: Okay, then let's go to question number three. How long should this study be? Cervical versus lumbar, fusion versus non-fusion.

We have like discussed this a lot. Unless the FDA is going to have an emotional reaction what I am about to say, I would like to say that we have discussed this a lot, and I don't know that we can resolve it better than it has been resolved.

Do you still prefer for us to go around the room and people make official comment on the question?

DR. WITTEN: I will defer to your chairmanship.

DR. BOYAN: My chairmanship -- wait. Dr. Nelson?

DR. NELSON: I think it is clear, when we are

talking about fusion products, we have got our goals of six and 12 and the various opinions that have been expressed.

However, for the non-fusion products -- artificial discs or whatever -- we have no idea what the follow up should be. We need more experience with those products before we can even give them any guidance.

DR. HANLEY: I would just make the comment that more scientifically validated studies require less follow up than less scientifically validated studies.

If you are able to put something together that is prospective and randomized, you don't need to do it as long.

If you have something that is how we used to do it when I was a kid along with my brother, and here are my results, it is going to take longer.

DR. BOYAN: I think that is well stated. Our guidance -- if I may state what I have heard during the day, our guidance would be that the study needs to fit the questions being asked.

If it fits it well, then the time frame that the study needs to be conducted in needs to be obvious and negotiable.

It does need to remain open ended, though, for the newer technologies that are coming through, because we simply do not know. Is that fair? Okay, next question.

What are our expectation for disc height

maintenance for devices that are implanted within the disc space. What are our expectation for vertebral height maintenance for vertebral body replacements.

Let's start this one with a spine surgeon, a certifiable spine surgeon. Dr. Cheng, would you start this one please?

DR. CHENG: I am not certifiable. I really don't think I have any comments on this or expertise, really.

DR. BOYAN: Let's go this way. You are next, Dr. Skinner.

DR. SKINNER: Having absolutely no expertise on this, I would have to say that I think for disc height maintenance, you would want to have something that was close to the previous disc height and something close to the previous vertebral height.

DR. YASZEMSKI: I will just reiterate what I said before. If the surgeon chooses disc height increase as part of his or her procedure, then that should be maintained with a small allowance for error in reading the radiographs.

Likewise, if a surgeon replaces a resection gap from vertebrectomy with a device of some sort, then that resection gap should be maintained at what was selected at the time of surgery.

DR. LAURENCIN: Nothing to add.

DR. ABOULAFIA: I agreed with Dr. Yaszemski before

he made his comment. I still agree.

MS. MAHER: Nothing to add.

DR. HOLEMAN: Nothing to add.

DR. DUCKER: The trouble is, with most fusions there is clearly some settling. I am not sure this is an important question.

It is either fused and you quit hurting or it isn't fused. So, how much you are maintained, I am a little bit more interested in whether you are typhotic or angulated, frankly.

If you settle straight, you are not going to hurt very much. I have got more fears on angulation and kinesis than I do on the settling.

Now, when you go into -- come later when we get into non-fused devices, which is question five, that is a little different.

DR. NELSON: No comment.

DR. HANLEY: I would just comment that the margin of error in reading the radiograph has been studied on many occasions about how many millimeters does the human eye fool you.

It is at least a couple of millimeters and it can be up to four millimeters. I don't think you want to be too strict on this.

If you count in natural subsidence of any space

implant, and your margin of error, you have got quite a swing there. I think if you start getting rigid, you may not like it.

DR. HACKNEY: If a manufacturer has an implant that they believe its function is to maintain disc height, and that is why you use it, or to maintain vertebral height, then in their IDE they should explain why a few millimeters variation in disc height or vertebral height are important.

Based on that rationale, you will be able to decide how to measure it and what magnitude of change you consider significant.

I don't think I can begin to define what magnitude of change would be important. It is not clear that it matters at all.

If someone says it matters, and that is one of the reasons for using this device, then the reason that they want to use it will make the answer to this question apparent and will lead the question that you are asking in your study.

DR. CLAUW: Nothing to add.

DR. BOYAN: Did we answer that to your satisfaction, FDA?

DR. WITTEN: Thank you.

DR. BOYAN: Question number five, the one that we have been waiting for. For non-fusion implants, as in disc

replacements, nucleus replacements and so forth, they are interested in knowing how we should go about patient selection, clinical success, radiographic success and what kinds of control populations should be used.

I am not going to run any more risks. We will just go ahead and go around the room. We will start with Dr. Aboulafia and then go to Dr. Laurencin.

DR. ABOULAFIA: I have no comments.

DR. LAURENCIN: I think that many of them are the same for the fusion implants, except, again, a greater emphasis on outcome variables in terms of functional performance and the P word, pain.

DR. YASZEMSKI: Dr. Boyan, you mentioned that the biologics are coming down the line. I think these are a little bit ahead of them but not too much far ahead of them.

I don't have any strong feelings one way or another except to say we should recognize that it is fairly new.

When they come, it will likely be perhaps just a few places doing them. I don't think the initial attempts will be widespread over many centers.

DR. BOYAN: I guess I would argue that they do need to be, some of these replacements do need to be considered now as certainly new materials, and there has to be some pharmacologic assessment in addition to the

functional assessment.

How that is done is, I think, definitely dependent upon the material that is selected. It does have to be done.

I don't think we can make an automatic assumption that the preclinical information will be identical to the human experience. Dr. Clauw?

DR. CLAUW: I would evaluate it exactly the same. I have already said that I don't think fusion is very important, so I don't think non-fusion is very important.

I think that pain and function should be primary outcome measures for these, just as they would be for a fusion device.

DR. HANLEY: We are really talking about intervertebral disc replacements here. I think the criteria for patient selection would be the same criteria that we use for cage implantation for degenerative disc disease, being predominantly one or two level disc disease, and most often not three level disease.

The selection criteria would be identical to those for that condition of the painful disc. Clinical success would be based upon the same criteria for pain, function and neurology as degenerative disc diseases.

Radiographic success would be measured by the same type of criteria that we use for joint implants -- total

hips and total knees with, if it is a metal backed implant, for instance, radiolucent lines and loosening and migration of the implant.

The control population might be easy here, because we have got cages.

DR. LAURENCIN: No comment.

DR. NELSON: I think this is where pain climbs from the back seat to the front seat. The radiology may stay in the front seat, but generally there is so much here that we don't yet know.

We don't really know what the guidance document needs to say.

DR. DUCKER: Basically, the pain selection and clinical success have been outlined. The radiologic success, though, in these is serial films that the device itself didn't collapse, fail or slide north or south.

Your follow up X-rays here, it is actually your X-rays and your CTs. Your MRs may be a bit tough.

Your control population, I think, has to be an ongoing just like any other study. It doesn't have to be randomized, but it has to be a concordant group of patients that you treat either you standard way with a fusion -- for example, in the neck or however you want to treat it in the lumbar area.

DR. HOLEMAN: No comments.

MS. MAHER: No comment.

DR. LAURENCIN: Maybe this is the time to talk about the randomized surgeon. Maybe if you have two procedures, maybe you have surgeons in a particular institution that one favors doing a procedure like this, one favors something more standard like the cage.

It might be appropriate to do a randomized surgeon and really do a randomized prospective trial.

You have got to have situations where those exist and are available to the same patient, and that is a key feature. It is certainly a valid design. It certainly can be analyzed very nicely.

It has the advantage that the surgeon probably believes in the procedure, whichever one you get randomized to, and that is very, very nice and very important.

DR. BOYAN: Thank you. Dr. Ducker?

DR. DUCKER: I know you want to do that, but it won't work. You develop a relationship with the patient. They have got to have faith that you believe in this, too.

If you go talking one way or the other, I just don't see where you can do that. You are going to say, this is available; do you want to do it or not. It is going to be easy to match that if we all do it right.

There are so many nightmares in randomization that it is just not worth reviewing.

DR. BOYAN: Any other comments?

DR. PERSENAIRE: One comment on the diagnostic criteria. My company is working on such a project. It was mentioned earlier today that the functional spinal unit is a multi-joint complex, and most devices in development replace only one of them.

So, in addition to this being the same level DBD patient, I think the additional criteria should be that the posterior elements should be in fairly good shape. That could be a question to the panel.

DR. BOYAN: Dr. Witten, have we adequately addressed the FDA concerns?

DR. WITTEN: Thank you.

DR. BOYAN: Does anybody on the panel want to take a -- I hate to do this. Let's save that question, Dr. Persenaire's question, until the end and see if we have time to address it, about the posterior aspects if you are working on the anterior, and the unit as a unit. It could be a philosophical discussion. Yes. You are going to go for it.

DR. HANLEY: No, I am not going to go for that. I am going to make a comment that generally speaking, we will ask for comments from the audience if we wish them.

I think this is a good time to ask the audience for comments. I think Dr. Zdeblick may have some knowledge

about intervertebral disc replacement and the things that we have been talking about.

If it would please the chair, we might ask him about his comments on the disc replacements. Is that okay, Madam Chair?

DR. BOYAN: That is okay.

DR. ZDEBLICK: I think the discussion regarding that has been excellent. I think pain is a valid criterion for success when you are talking about joint replacement. It should be monitored.

I think the radiographic criteria would be stability, meaning the implant hasn't migrated, maintenance of motion, meaning you didn't get an inadvertent fusion, and absence of problems such as erosion of a nearby vessel or infectation of the nerves that are nearby.

I think other than that, like Dr. Hanley said, the patient population should be very similar to those with degenerative disc disease.

I think one additional will be the end point of a previously performed fusion. I think many surgeons are looking toward artificial discs as a way to stop the adding on phenomenon, having one level break down above a previous fusion.

That adjacent level to a previous fusion may be an additional entry criteria that we don't normally do fusion

surgery on.

Otherwise, I also agree with Dr. Boyan's suggestion that monitoring of the material would be important.

Certainly these devices would use novel materials. They may generate debris and they may generate distant migration, and that has to be monitored as part of these studies. I think the discussion regarding those has been excellent.

DR. BOYAN: Question number six. For patients with tumors metastatic to the spine, we need to consider the control populations, clinical parameters, radiographic parameters and success criteria.

Dr. Aboulafia, because you mentioned this earlier, you get to start the discussion.

DR. ABOULAFIA: I guess I would only have to repeat what I already said. I guess, the control population I would borrow, again, from Dr. Larntz, which is all others.

There are a lot of other alternative methods for treating patients with either pathologic fractures of the spine or pending pathologic fractures of the spine.

Whatever those methods are, all of those can serve as controls, just like Dr. Larntz suggested for a different situation earlier today.

Clinical parameters, again, it is really -- I

would look more at pre-operative and post-operative function, ambulatory status, ability to get around a pain control or narcotic requirement. Those probably would be reasonable parameters.

I don't think you have to look at much more than what their preoperative status was, or what their pre-morbid status was.

If someone came who had an acute neurologic deficit, you might look at what their status was a week before they were admitted to the hospital with a neurologic deficit.

Radiologic parameters, again, there is stability and nothing else. You aren't looking at a fusion. You are looking to try to -- when I say stability, the patient doesn't have progressive kyphosis or lordosis or deformity.

Success criteria are really patients being able to have relief of pain and mobility. So, functional status equal to what they were preoperatively or better would be the criteria that I would use.

I think it is pretty straightforward and a lot less stringent and a lot less difficult to acquire that data than what we have been looking for some of the other patient populations.

DR. BOYAN: Thank you. Are there any other comments that people would like to add to this? Yes,

Dr. Skinner?

DR. SKINNER: Just one on the control population. If the control doesn't have a surgical procedure associated with it, I worry that it is going to be too biased against the experimental procedure.

You will tend, in a metastatic tumor to the spine, to operate on those that are most dangerous, most difficult, most complicated, and you will tend to treat with radiation or whatever, chemotherapy, those that aren't so bad. There could be a bias there if the other treatment is not a surgical treatment.

DR. ABOULAFIA: when I said control population, all others, I meant all others surgically treated. I think the reason I keep it simple like that is because you will find it very difficult to select criteria for when to do an operation versus when to radiate versus when to embolize.

A lot of those things depend on patients' preferences, patients' lifestyles, where patients live, how easy it is for them to get to the radiation therapist.

They may be in a time period in their life where they may not want to spend a lot of time traveling to and from the radiation oncology department.

So, I guess for control, would it work better, Dr. Skinner, if I said all other surgical procedures?

DR. SKINNER: Yes, I agree with you.

DR. DUCKER: This is one place that will make a statistician happy. This is one place where we can randomize in a group of patients.

I wouldn't have any reservations comparing a new device to what we have been doing, whatever that is, because you have got very defined end points here.

I mean, you have got a mortality issue much less the neurologic function. There is a tremendous pain problem. So, you do have your one day here.

DR. CLAUW: Two comments. One is that I think in reality it is actually very difficult to randomize because you have to stratify by tumor type.

There are not enough of these patients around in any one center of the same tumor type to really be stratifying both by extent of disease and tumor.

Someone with pulmonary metastases will act entirely different than someone with breast metastases.

The other thing I would say is, you have to be really careful in this instance about the outcome measures you choose.

The problem with generic outcome measures is that they are going to be influenced by the rest of the cancers that the person has.

The problem with disease-specific outcome measures is, really, you may really not be having an impact just on

I would suggest that one needs to take into account not only the diagnosis but disease severity and their cancer stage, as well as other treatments.

Doing any kind of studies in this setting is very, very difficult to do, but you need to take those other factors into account.

DR. ABOULAFIA: That is one of the reasons that I brought up the point of looking at their preoperative status and postoperative status and not taking it much further than that.

A 40-year-old woman with a solitary focal metastatic lesion to the lumbar spine is very different than a pulmonary patient who has got multiple osteocytes and poor lung volume and functional status preoperatively.

I thought that was probably the easiest way, and most meaningful way of capturing that information.

DR. HACKNEY: I agree, that the radiologic evaluation is fairly straightforward, mechanical stability of the spine and alignment, and mechanical integrity of the assembly and canal compromise.

I think one other factor that hasn't been mentioned for these tumors is how quickly the patients respond.

Although there are some patients who have metastatic disease of the spine who live for a considerably

long period of time, in most cases one of the goals of surgery is the fastest way to give them enough stability in their spine to get them up and around for what is left of their lives.

A technique that works great, but doesn't work great for three months, isn't really a useful technique for this patient population.

One of the other goals will be to get patients who were walking before, how soon after surgery are they up and around.

That obviously will be heavily impacted by how sick they were before they went into the OR. It is something that you might be able to average out if you could sort of randomize against the potential very large number of patients that you could enroll.

DR. BOYAN: FDA? Yes, Dr. Witten?

DR. WITTEN: I do have one question. I know this is a difficult area. We had a long discussion about study duration previously.

I am just wondering if there are any comments about a reasonable time point to look at success for this kind of study.

I realize that it may vary depending on the specific population under study, but just some broad opinions about this.

DR. HANLEY: First, I will just say I do not think you can study this well. All these patients are different. There are so many variables involved and you get into the compassionate use versus prospective studies and all these things.

I think trying to make something scientific that is very difficult to make scientific is difficult to do. If you are going to look at end point -- and there are not enough patients at any one place either.

A reasonable approach for timing, one year or until demise is the best I could come up with.

I personally think you should just carve it out and only address it briefly in the document and state that you can't apply the criteria that we are trying to apply these other things to.

DR. CHENG: This is one of those obvious circumstances you can't study for two years. In our prospective study of pathologic fractures, half our patients were dead at six months.

Either we had a pretty bad patient population or pretty bad doctors. So, you have to follow the pain relief longitudinally every month, is what will need to be done.

DR. BOYAN: I think in some of these materials you do need to be conscious of the fact that, especially if they have pharmaceuticals included in the material, that some of

these pharmaceuticals have very deleterious effects to the cells that you want to have come back, which are the osteoblasts.

That needs to also be taken into consideration, that in the review of the preclinical data, FDA, perhaps, before they plan to go forward, that they maybe get a more thorough assessment of some of the biological data that they are presented with.

There are different kinds of questions that should be addressed than simply the standard set of tests that normally are used to look at cytotoxicity.

All right, we have done that one; yes? Number seven. This is getting close. Question number seven, health related quality of life.

This one is going to start with you, Dr. Holeman. This is what kinds of instruments should be used to examine that, SF36, SF12, what kinds of information should be captured and how should we use that information.

DR. HOLEMAN: Basically, I am going to comment on what I know about the SF36 and the SF12. I do feel that they are valuable instruments to collect the data.

I do feel that we do need to have information on the quality of life, especially since the discussion this evening has focused on whether or not pain should be primary or secondary.

If we say that pain is secondary and fusion becomes primary, then what will that say for the patient relative to the way the patient sees the outcome of the surgery. That will definitely be needed.

I think it will add to how we utilize or how we say, and to what extent we say that that procedure has been effective for the patient.

It gets to the next question. It plays into satisfaction and how the patient views their procedure.

DR. BOYAN: Any other comments? Yes, Dr. Clauw.

DR. CLAUW: The SF36 can be scored in at least 30 or 40 different ways to give different measures. It really does do both health related quality of life as well as health related patient satisfaction.

Even though I deal with pain and I deal with sort of mooshy outcomes all the time, I think that sometimes you can go too far in developing and having yet a different measure for patient satisfaction than the SF36.

I think that if that is given as sort of a generic measure of health status, you can get a great deal of information out of that, with well validated sub-scales within the SF36 to look at a number of different constructs within this class.

DR. BOYAN: Are there any other comments? I know Dr. Witten is going to ask us for suggestions of other

instruments. She didn't. Okay. Yes, Dr. Witten?

DR. WITTEN: However, I do have a question. My question is, related to the ability of the health related quality of life measures in this question to be responsive to clinical change as might be seen in these kinds of surgical procedures performed on these patient populations.

In other words, it is validated in the populations, but will a difference that is a clinically meaningful difference to the patient, be likely to be demonstrable on these instruments.

DR. BOYAN: Anybody want to take that question on?

DR. CLAUW: Yes. You might use a different numerical change in SF36 to indicate a clinically significant difference and given different types of interventions.

It is very responsive to different types of surgical interventions, medical interventions, and well used in different kinds of outcome studies. It is not just used to look at people who are at a single point in time.

Then the issue becomes, it goes back to what we were talking about before with things like function and pain.

What do you say? Do you say 20 percent improvement? Do you say 10 percent improvement? That is where there is not unanimity in nearly any field about what

is a clinically meaningful change in one of these outcome measures.

DR. NELSON: A question for Dr. Clauw. Are you familiar, though, with the SF36 or 12 being useful in spine.

I have found in hand surgery that some of the instruments that they have out there that are very well validated and they are very popular, they don't do anything at all for particular types of problems.

I think the FDA's question is, these may be great measures. Are they great measures for spine.

DR. CLAUW: What I would say is that, of the generic health status measures -- again the work by Bobadier(?) and Beaton, there are two different articles in two different journals in the last year or two -- the SF36 performed the best, both respect to reliability, validity and change in an individual.

It is not as good -- it will never change as much as a disease specific outcome measure, because there is more going on in the person than what you are operating on.

There is some reason to do both disease specific and generic outcome measures. If you are going to use a generic outcome measure, the SF36 is probably about the best you are going to get.

DR. BOYAN: Any other comments? Yes, Dr. Larntz.

DR. LARNTZ: The SF12, you know, is a subset of

the 36. My experience with it is that if you have big effects, you can find it with the SF12. The SF36 is better, has more questions, more time to take, too.

Euroqual is a very simple one that works very well for lots of circumstances. It is very simple and has a small number of questions, smaller, I think, than the SF12. Some people have said that it actually works just as well.

DR. BOYAN: Question eight. If we followed Mr. Demian's instructions, we could stop here. Then we got mail. So, we have to go to nine, since this is the penultimate question, patient satisfaction. How do we capture this. How do we use this.

I always ask for these kinds of questions Dr. Holeman. Why not.

DR. HOLEMAN: I think my comment would still be the same as I said with question number seven, though, that the patient satisfaction, I cannot name an instrument that would actually measure that, other than what you will get from the SF36 or the SF12.

Still, we do need to have the patient perception of the outcome. I think the patient satisfaction will yield that data.

To the extent that we find that it may not be statistically significant with subjective data, this will give some indication of how the patient perceived the

outcome of their surgery.

DR. BOYAN: Anybody over here want to make an additional comment? Yes, Dr. Ducker?

DR. DUCKER: One caution. The SF36, while not being as specific -- I agree completely with Daniel -- will give you some of the patient satisfaction.

If you ask just patient satisfaction, let me warn you about an article that we are about to publish on cervical fusions for neck pain.

I mentioned it earlier. The patients like it. They were pleased they had the operation, but their pain scales didn't move. So, there are limits on patient satisfaction.

I would put it near the bottom of my list of things I want to know. I am more interested in disease specific and the SF36, which I can derive back to patient satisfaction.

DR. BOYAN: Okay, FDA, what is the story? Are we okay? Okay, question number nine.

DR. ZDEBLICK: Is it appropriate for me to ask a question?

DR. BOYAN: Sure, go ahead.

DR. ZDEBLICK: It goes back to the point I raised very early on. I don't want anybody to misunderstand my position on this, or the surgeon's position.

We don't feel that pain is unimportant. By all means, I spend every day of my life treating patients' pain. That is what I see in the office; that is what we talk about; that is what I come up with procedures to help.

You have to decide what hat you are wearing at this table. I am wearing my surgeon's hat at home and I am trying to treat pain and I am very acutely aware of what pain is doing.

As the FDA, you are here to determine whether the surgeon's choice of treatment is safe and efficacious. I don't believe that that entails, as a success criteria, pain relief.

If a surgeon decides that a fusion will help that patient, then fusion should be the success criteria. The same with an artificial disc. If that is what the surgeon chooses, and that artificial disc is going to function as it is supposed to, the pain relief is so dedicated to the medical profession that now you have moved away from determining a product's safety and efficacy to determining a physician's choice of treatments efficacy.

That is a big step. If the FDA wishes to take that step and this panel helps them, I think you have to be aware of the consequences of that step.

It doesn't mean that I downplay pain. It doesn't mean you shouldn't follow pain. It doesn't mean that you

shouldn't report an analog scale of how pain did in these procedures.

We should not use pain as our determination of whether that implant is successful or unsuccessful. Thanks.

DR. BOYAN: I am not sure what to do with that. It goes fundamentally against the chairman's deep and inner feeling that the surgeon is not always right and that the patient has at least a 100 percent commitment to the outcome as the surgeon does.

DR. ZDEBLICK: So, what you are saying is the committee here should regulate the surgeon's practice of medicine.

DR. BOYAN: I am not saying that. I think that you do -- it is a philosophical issue and it is certainly open to discussion. Probably that is one you and I should do out in the hallway.

It is one where the patient's contribution to the outcome is very important and success is not only whether or not it was medically correct. Success is also whether or not the patient thinks it is medically correct.

It is not regulating you. FDA is not regulating, and this panel is certainly not regulating you.

With that, I think unless there is an overwhelming need for someone else to make a comment, then I think we should probably continue that one outside.

Is there an overwhelming need for anybody besides me to have an emotional moment? Okay, no. Number nine.

Subsequent surgical interventions, removals, revisions, re-operations, supplemental fixations. How do we prospectively define the adverse events and failures. How do we define safety and efficacy in terms of these events. Do we believe that the nature of the spinal assembly dictates how adverse events are to be viewed and, if so, how.

This is the last question. So, let's just do it officially. Let's start with Dr. Clauw and move around.

DR. CLAUW: I will pass. I am not a surgeon.

DR. HACKNEY: I am not a surgeon.

DR. HANLEY: Generally speaking, if you have to re-operate on somebody you have at least some semblance of a failure there, since you were anticipating operating on them once. These things do occur. We do do re-operations.

I think in the IDE proposal, the study people will have to define what the criteria for success and failure are with regard to removal or revision of an implant.

It doesn't necessarily mean automatically that if you remove an implant it is a failure, but many times it will be.

All of these things are points against you, in the scale of whatever success is. If you have to remove it,

obviously something went wrong. If you have to revise it, obviously something went wrong or you didn't do the right thing before.

If you have to re-operate, something went wrong. Supplemental fixation, something went wrong. If the patient doesn't want the implant in them, something went wrong.

So, those are all not absolute criteria for failure, but they need to be addressed in the document with regard to how many points they are going to take off your degree of difficulty with this particular implant, using the diving analogy. They will have to be anticipated and be part of the deal.

DR. NAIDU: I think that if you are going to remove the implant, if you are going to re-operate or revise, I think by definition it is a failure.

As far as defining safety and efficacy, I will pass on that question.

Do you believe that -- I will pass on that question, too.

DR. LARNTZ: The only thing I would do with these, I presume -- we hope there aren't too many. If you are in a comparative trial, you want to compare the time to these, if there are a considerable number, and see how long the implants last, and so on. So, time to event analysis comes to mind with these kinds of events.

DR. NELSON: No comment.

DR. DUCKER: I don't think you can ignore these facts. This is why you have to have concurrent controls, not necessarily randomized, to what you are doing.

Basically you have got to have what are called the adverse reactions. These include the instance of infection and the significant neurological sequelae.

You are going to measure some other clinical assessment of whether they are having pain or not, and whether the device has to be removed or not or supplemented.

The final thing is how often you have to go back and see the doctor. We have used that as a good measure of the success of devices.

If you put a device in and they disappear and they are happy, that is quite different than somebody who has a device who keeps coming back to see you to get his pills renewed or some problem like that.

There is another way of measuring that. I think these have to be included in some way in the document.

DR. HANLEY: Can I ask you a question? What do you think about, if you have to remove a device, is that automatically a failure for that individual patient, that individual device?

DR. DUCKER: It practically almost is. Either that or you have to supplement it. I have got one next week

that I am going to have to supplement. I won't tell you where it is.

DR. HANLEY: I just want your opinion. I don't really know how to address it. It is a very difficult issue to address.

Certainly if you have to remove a device or revise a device, it certainly isn't going to assist you in your success rate.

DR. DUCKER: No. It is an adverse reaction. In other words, what are the problems, and that is it.

DR. BOYAN: Let's go around and then we will come back.

DR. HOLEMAN: No comments.

MS. MAHER: My only question is -- and it is a question, really, not a comment -- does that mean that if a device's end point was to fuse the spine, and the spine is fused and the patient is fine, but the implant has become loose at some point in the future, and you go in to take it out and the patient is still fused and still fine, you would diagnose that as a failure?

DR. HANLEY: No, I was saying I don't know how to deal with that. I would call it a half failure, I guess.

DR. DUCKER: I would call that a failure. You know, if they got loose, there is something wrong. We have taken -- I haven't recently, I have gotten smarter -- but

people with some persistent back pain, we take out the devices to make them happier, and it doesn't work.

You are no better than a 30 percent improvement rate, which is no better than a control. So, any time I am redoing it, something isn't right.

DR. NAIDU: Can I just add something? I think in any other part of the body, the hip joint, the knee joint, if you take out the implant, it is a failure.

DR. BOYAN: I am going to have to ask for clarification here. I guess my question is the same as Ms. Maher's which is, if you have fusion and the goal of the device was to achieve that, and then the device comes out, why is that a failure of the device.

DR. ZDEBLICK: I would like to address that same point. It is not a failure every time you take a device out. If you have an ankle fracture for instance, and the ankle fracture is healed, and the device is prominent, then you go in and make a small incision and remove the screw.

That device worked perfectly well. It was a successful operation and device. The same with pedicle screws.

Many of those patients that were very thin had a solid fusion but had tenderness over their screws. I disagree with Dr. Ducker. I do have some patients that get better, then, if you go back and take those screws out. The

fusion is great and you repair their muscles.

The same with revisions. Not all revisions are failures. If you, for instance, the day after surgery, take an X-ray and notice that one of the cages was 30 degrees malrotated, you tell the patient and you go back the next day and you turn it 30 degrees, and now it is lined up right and they go on to heal successfully, that is not a failure, even though they required a revision of procedure.

I would caution that not all revisions and not all removals are failures. I would also caution that we don't have to report all adverse events.

If a patient breaks their arm six months after a spine fusion, right now that has to be reported. That doesn't make any sense to me. I would caution against making always statements and try to be somewhat flexible in how we report these events.

DR. BOYAN: Coming around over here.

Dr. Aboulafia?

DR. ABOULAFIA: I agree with Dr. Zdeblick. The example I was going to use was an intermedullary rod. We put intermedullary rods in femurs all the time. They heal, they do fine and some patients want it out.

Why do they want it out? They are afraid maybe they are going to break their femur again and with the rod in, it will make any additional surgery more difficult.

That may be one reason.

They may do it because they think the rod is causing them pain, which may or may not be true, but the device served its purpose.

I don't think that removal of a device, by definition, is a failure.

Then with Dr. Zdeblick's second example that if you go back and revise the device on post-op day zero or post-op day one, because it is mal-rotated, those are addressed in every IDE.

That is not a device failure. It is a failure of the procedure, and that is device related or not device related.

We could argue about whether that is device related or not. I think most of us could agree that it is not device related. It is the implantation of the technique used of the device.

The other thing is, failures and adverse events are two different things. Patients can have mechanical failure of the device and not have an adverse event.

We see intermedullary implants, again, to use the same example. You rod a femur or a tibia. It develops a delayed union, the rod breaks. They sit around and they wait for a couple of months for surgery, and it heals.

There is no adverse event but there is a failure

of the device.

The other thing was the example that Ms. Maher brought up. If everything is going fine and you have a union and, again, that is when the device has failed, I think that is a mechanical impossibility. If I am wrong, Dr. Zdeblick can correct me. I am sure he knows a lot more about spine fusion than I do.

If there is a bony fusion around the cage, there shouldn't be mechanical forces placed on the cage to allow it to fail. So, I think that is a hypothetical that will never happen.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: I have nothing to add.

DR. YASZEMSKI: I will add that I believe it is important to follow all removals so that one can assess why it came out. It is not always a failure.

To add to other examples that have been given, consider a posterior spinal fusion device with the rod is cut a little bit long and is impinging on the facette joints above.

The fusion gets solid and the patient perhaps has pain and extension as the facette joints rub against the rods. If you take the rods out, the fusion is solid and the pain goes away. I would not consider that removal a failure.

I think that some removals can be failures and

they should all be followed.

DR. SKINNER: I agree with Aboulafia. If you practice in California, you will get a patient eventually who comes in and says that they want their intermedullary rod removed because it causes headaches, and it has nothing to do with it.

DR. CHENG: Perhaps this is a case of failure or success being too harsh a term. I think all effects -- the FDA probably wants to know about all the effects of the device, whether it is good or bad.

If you remove a device because it is big and bulky and hard to live with afterwards, the FDA should know about that.

I would err on the side of over-reporting. If a patient breaks their arm, I don't think the committee is going to give advice related to that, but the FDA should probably know about that.

I think if you are going to write a guidance document, I would err on the side of over-reporting.

DR. SKINNER: One comment? If the patient does break their arm, that could have an effect on their SF36, and that could help explain why their SF36 changes.

DR. PERSENAIRE: As a general observation, until today, all labeling of pedicle screw systems still requires the removal after a fusion has healed.

DR. BOYAN: So, there we have it. What I think we should do now is, we have reached closure for our part. Ask the FDA, did we address their concerns on question number nine specifically and in general?

DR. WITTEN: Yes, thank you, and thank you, yes.

DR. BOYAN: With that bright note, there is more here. Before we officially close this event, let's see what I have to do here. Yes, I have got my instructions.

I would like to make a comment that is just from a personal comment, and compliment Dr. Panitch and Sami Allen on making the attempt to put together a document of this complexity and to have done it as well as you did.

I would like to thank the speakers for hanging in here until the end and participating in the discussion. Your contributions were really quite helpful.

All of you on the panel, I would like to thank you for bringing your different areas of expertise to this. I think it would be wonderful if all guidance documents had this kind of review and this kind of effort put into it by all the interested parties.

Now, I gather that the FDA is interested in having additional comments if people in the audience want to add your comments. There are copies of that draft outside, I believe, and you are free to pick them up and scribble on them and hand them to an FDA person or send them by mail or

by e mail. Any kind of advice you can give is always useful to them.

This concludes the recommendations of the panel for the preliminary background document for spinal assembly.

MR. DEMIAN: Now we are going to proceed with another open public session. I am going to turn this back over to Dr. Boyan.

DR. BOYAN: We have another open session. So, here we go. We will now proceed with another open public hearing session of this meeting.

Agenda Item: Open Public Session.

DR. BOYAN: I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone, as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing of the meeting disclose whether they have financial interest in any medical device company before making your presentation to the panel.

In addition to stating your name and affiliation, please state the nature of your financial interests if any.

Is there anyone here who would like to address the panel?

DR. NELSON: Madam Chairman, what is the subject?

DR. BOYAN: Anything that you would like to

address the panel on. This is an open discussion.

So, seeing that there is no one who wishes to address the panel at this time, I am going to turn the meeting back over to Mr. Demian.

MR. DEMIAN: At this time I would like to thank all the panel participants for their time and effort and their energy in reviewing this material, and for their participation on this FDA panel. All your efforts are truly appreciated.

At this time I would like to remind all panel members that if you want the review materials and any notes that you may have taken destroyed, please leave it in front of you and place your name card over it.

Please note that this information that will be presented to me, the executive secretary, will be placed into the record.

DR. BOYAN: On behalf of the FDA, I would like to thank the entire panel. This meeting is adjourned.

[Whereupon, at 4:43 p.m., the meeting was adjourned.]