UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OFFICE OF DEVICE EVALUATION

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DENTAL PRODUCTS PANEL

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MEETING

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THURSDAY,

AUGUST 22, 2002

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The Panel met at 8:00 a.m. in the Whetstone/Walker Rooms of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Leslie Heffez, Chairperson, presiding.

PRESENT:

LESLIE HEFFEZ, D.M.D., M.S., Chairperson

KRISTI ANSETH, Ph.D., Member

PRESENT (Continued):

PETER BERTRAND, D.D.D., Consultant

RICHARD BURTON, D.D.S., Consultant

DAVID COCHRAN, D.D.S., Ph.D., Member

JAN E. FAULK-EGGLESTON, D.D.S., Consultant

ELIZABETH R. HELMS, Patient Representative

EDMOND R. HEWLETT, D.D.S., Member

ELIZABETH HOWE, Consumer Representative

JANINE JANOSKY, Ph.D., Consultant

STEPHEN LI, Ph.D., Consultant

MARK PATTERS, D.D.S., Ph.D., Consultant

ELIZABETH DIANE REKOW, D.D.S., Member

DANIEL SCHECHTER, J.D., Industry Representative

JON B. SUZUKI, D.D.S., Ph.D., Member

PAMELA D. SCOTT, Executive Secretary

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:04 a.m.)

MS. SCOTT: Good morning, good morning. I'd like to welcome everyone to the Dental Products Panel meeting.

Before we get into our topic for today I would like to introduce our panel, and then I have a conflict of interest statement to read into the record.

My name is Pamela Scott. I'm the Executive Secretary for the Dental Products Panel.

Our Chair is Dr. Leslie Heffez. He's Professor and department head of oral and maxillofacial surgery at the University of Illinois at Chicago.

And as I call out the panel members and panel consultants' names, if you could just raise your hand so that people know who you are, we have

Dr. Kristi Anseth. She's Patten Associate Professor with the Department of Chemical Engineering at the University of Colorado.

We have Dr. David Cochran, who's Professor and chair of the Department of Periodontics at the University of Texas, Health Science Center at San Antonio.

We also have Dr. Edmond Hewlett, who is Associate Professor in the Division of Cardiology and Restorative Dentistry,

University of California at Los Angeles School of Dentistry.

We have Dr. Diane Rekow, who is Director of Translational Research and Professor of Orthodontics with the New York University College of Dentistry.

We also have Dr. Jon Suzuki, Professor, School of Dental Medicine at the University of Pittsburgh.

Our consumer representative is Ms. Elizabeth Howe. She's Outreach Coordinator with the National Foundation for Ectodermal Dysplasia

Our industry representative is Ms. Daniel Schechter. He's General Counsel with Parkell, Incorporated.

We also have Ms. Elizabeth Helms, who is serving as our patient representative for this panel. She is President of the TMJ Society of California.

We also have Dr. Peter Bertrand, who is the Director of the Orificial Pain Clinic and specialty advisor for oral facial pain and TMD with the National Naval Medical Center.

We have Dr. Richard Burton, who is Professor of Oral and Maxillofacial Surgery with the Department of Hospital Dentistry at the University of Iowa Hospital and Clinics.

We also have Dr. Janine Janosky who is Associate Professor, Division of Biostatistics with the University of

Pittsburgh, Department of Family Medicine and Clinical Epidemiology.

We have Dr. Stephen Li, who is President of Medical Device Testing and Innovations.

We also have Dr. Mark Patters, who's Chair of the Department of Periodontology, College of Dentistry, University of Tennessee.

And we have Dr. Jan Faulk-Eggleston, Chief of the Oral and Maxillofacial Surgery Service with the Brooke Army Medical Center.

At this time I'll read into the record our conflict of interest statement for the Dental Products Panel meeting of August 22nd, 2002.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety.

The determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest.

The agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government.

We would like to note for the record that the agency took into consideration a matter regarding Dr. Stephen Li, who reported a past interest in a firm at issue, but in a matter that is not related to today's agenda. The agency has determined that he may participate fully in all deliberations.

In the event that the discussions involve any other product 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 interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firms whose product they may wish to comment upon.

And before I turn it over to Dr. Heffez, I also would like to introduce Dr. Susan Runner, who is the Branch Chief of the Dental Devices Branch within the Division of Anesthesiology,

Infection Control, General Hospital, and Dental Devices.

I got that right. We just changed our division name.

(Laughter.)

MS. SCOTT: Dr. Heffez.

CHAIRMAN HEFFEZ: I'd like to proceed to the open public hearing. Those who wish to speak should state their name, state their affiliation, and any specific financial interest.

We've reserved 30 minutes for this period of time, and I'll ask if there's anybody in the audience who would like to come to the podium.

(No response.)

CHAIRMAN HEFFEZ: Nobody had signed up previously, despite the advertisement of this meeting, and I don't see anyone coming to the podium. So we'll proceed then to the industry presentation.

The industry presentation will last one hour, and I will hold you to the time.

MR. PRATT: Good morning. My name is Joel --

CHAIRMAN HEFFEZ: Excuse me. Excuse me, sir.

Prior to your start, I would just want to have Pamela Scott list the members and who are voting members for this committee.

MS. SCOTT: I apologize. I need to read into the record those panel consultants who are deputized to vote during this meeting.

Appointment to temporary voting status, pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27th, 1990, as amended April 20th, 1995, I appoint the following people as voting members of the Dental Products Panel for this panel meeting on August 22nd, 2002:

Dr. Peter Bertrand

Dr. Richard Burton

Dr. Janine Janosky

Dr. Stephen Li

Dr. Mark Patters

Dr. Jan Faulk-Eggleston

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting.

Signed, David Feigal, M.D., Director, Center for Devices and Radiological Health, August 19th, 2002.

Thank you.

CHAIRMAN HEFFEZ: Mr. Pratt, you may begin.

MR. PRATT: Thank you.

Good morning. I am Joel Pratt with Lorenz Surgical, and I will briefly show you a couple slides to start our presentation.

This is sponsored by Biomet, Incorporated. Biomet consists of a number of different subsidiaries that address different orthopedic and musculoskeletal specialties. So within that framework, as you can see by the customers and their specialization, this would be considered a Lorenz product.

Attending today from management are those listed from both Biomet and from Lorenz, several of whom will be speaking. We have two clinicians present: Dr. Peter Quinn from Philadelphia, Pennsylvania, and Dr. Douglas Sinn from Dallas, Texas.

We are asking approval for the Lorenz TMJ, which is a total joint replacement for the temporomandibular joint, and the indications we are pursuing are arthritis, malignancy, benign neoplasms, functional deformity, revision procedures, avascular necrosis, ankylosis, degenerated or resorbed joints, fracture, multiply operated joints, and developmental abnormality.

MR. ROMAN: Good morning. My name is Shawn Roman, and I am the development engineer currently working with the TMJ

total joint replacement system at Walter Lorenz Surgical.

I will be presenting a description of our device, as well as a summary of all of the mechanical testing that has been performed.

The TMJ total joint replacement system is a two component system that comprises mandibular fossa components, as well as a glenoid fossa component. The purpose of the fossa component is to replace the glenoid fossa of the temporal bone.

Our fossa components are machined from ultra high molecular weight polyethylene and are offered in three sizes, small, medium, and large, both the right and left side anatomy.

We currently offer two different designs in the sizes mentioned. The original design included a post on the superior surface of the implant. We added a second design without the post in February of 2002, and both designs are secured to the zygomatic arch using self-tapping, two millimeter diameter fossa screws made from Titanium 64 alloy. We also offer 2.3 millimeter diameter crews as emergency screws.

This slide shows the difference between the two designs. The design on the left obviously has a small post protruding from the superior surface of the implant. This post was included in the original design to act as an additional

anchoring method when using bone cement or other approved cranio-maxillofacial filler materials to fill voices between the fossa prosthesis and the glenoid fossa bone.

Both designs include an undercut groove on the superior surface of the implant, which also offers a securing area for bone filler material.

So, therefore, both designs can be used with or without filler material. It has been found that the design without the post is easier to place and requires the removal of less bone.

The purpose of the mandibular components is to replace the articulating mandibular condyle located at the proximal end of the mandibular ramus.

We currently offer three different designs or -- I'm sorry -- our mandibular components are machined from cobalt-chromium-molybdenum alloy. The ramal portion of the mandibular component has a roughened titanium plasma spray coating on the medial surface. This plasma spray coating consists of the Ti-64 alloy.

We currently offer three different designs: a standard, narrow, and offset. I will go into these in a little bit more detail with the aid of some slides, but all three designs are offered in five different sizes for both the left and right

side anatomy.

We started with the narrow design, added the standard design in January of 2000, and added the offset design in February of 2002.

All three designs are secured to the mandibular bone using self-tapping 2.7 millimeter diameter mandibular screws made from Ti-64 alloy. The 3.2 millimeter diameter screws are offered as emergency screws.

Here you can see the difference between the standard design and the narrow design. As I mentioned, we started with the narrow design. We added the standard design in January of 2000 to add additional screw hole options to allow for placement of the mandibular screws in the best bone possible.

This slide shows the difference between the standard design and the offset design, the only difference being that on the standard design the spherical head is offset to the medial side of the ramal plate. In the offset design, the spherical head is offset to the lateral side of the ramal plate.

The offset design was added to allow for medial lateral or to accommodate for medial lateral discrepancies between the fossa components and the mandibular components.

This is a list of a summary of all the testing that

was completed, all of the mechanical testing completed on these joints. I won't cover these in detail here because I discussed them in detail throughout the rest of the presentation.

Basically we performed three different series of fatigue testing to insure that the mandibular fossa construct could withstand the loading seen in the TM joint.

The same testing protocol was used for all three series of testing. Basically the protocol consisted of cyclic compressive testing, compressive loading of the mandibular component against the fossa component.

We incorporated three different conditions into the testing protocol to simulate worst case situations. First of all, the mandibular component was secured below the center line of the first screw hole to simulate a patient with a large portion of the ramus removed or missing.

The mandibular component was also tilted at ten degrees to induce a large bending moment in the ramal plate, and we selected a maximum load of 145 pounds because this loading was documented in the literature to be the loading seen in patients with normal musculature that had not undergone previous TMJ surgeries. This load would obviously be excessive for patients who had undergone TMJ surgery.

This is just a schematic of the test set-up. The mandibular component was potted to the bottom test fixture, fossa component potted to the top test fixture. The bottom test fixture was held stationary while the top test fixture was cycled at ten to 30 Hertz.

I included this slide just to show that there was clearance milled into the top test fixture to allow or to accommodate for the post on the fossa component. The area around the post was -- there was bone cement placed in the area around the post to simulate surgical application in all of the fatigue testing done.

In the first series of fatigue testing, we tested the original design of the components, tested five different joints. All of the five joints made it out to ten million cycles with no failures.

Although in this first series of testing bone cement was used, the condition of the bond cement after the testing was not documented. So we ran a second series of fatigue testing that looks specifically at the effects of fatigue on the bone cement.

Another five samples were tested. All five of the joints made it through ten million cycles with no failures, and there was no fragmenting or chipping of the bone cement noted.

The third round of fatigue testing looked at design enhancements that were made to the mandibular components. These design enhancements included adding the titanium plasma spray coating to the medial side of the implant and also increased the screw holes slightly in diameter.

Another five samples were tested. Again, all five samples made it to ten million cycles without failure.

We performed static testing on the mandibular component to determine the amount of force required to fracture the condylar neck of the design, and in this testing the mandibular component was fixated to bovine tibial bone using four 2.7 millimeter diameter mandibular screws.

A direct force, direct Allen force was then applied to spherical head until failure of the component. The failure mode that was seen was not fracture of the condylar neck, but rather the neck portion bent with no breakage at 576 pounds.

This loading or these results were deemed acceptable because this loading is three and a half times larger than the 145 pounds joint loading discussed earlier in the fatigue testing.

We also performed pull through testing on the fossa screws to determine the amount of force required to pull them through the fossa flange. In this testing, test specimens

representing the fossa screws were pulled through a polyethylene sheet made of the same material as the fossa component. This polyethylene sheet was the same thickness as the fossa flange.

Basically a downward force was applied to the test specimens until they were pulled through the polyethylene.

This just shows that there was clearance underneath the fixture to pull those test specimens through.

They pulled through at an average load of 80 pounds. This was deemed acceptable because this was well above what would be seen in vivo.

We also performed compressive testing on the fossa flange to determine the amount of force required to fracture the flange. In this testing, we attached the fossa component to wooden blocks using only two of the 2.0 diameter fossa screws.

A direct force was then applied to the articular surface of the fossa component.

This is a close-up just showing that we simulated a worst case by not supporting the side of the fossa component opposite the articular surface.

The failure mode that was noticed during this testing was, again, not fracture of the fossa or fossa flange, but rather the fossa flange collapsed or bent at an average load of 83 pounds.

This, again, was deemed acceptable because this was a worst case test in vivo that you would have the support of the temporal bone on the side opposite the articular surface.

The final mechanical testing that was performed was pull-out testing on the 2.7 millimeter mandibular screws. In this testing, the mandibular screws were inserted through a test fixture into bovine cortical bone. Then an upward force was applied to the test fixture until the screws were removed from the bone.

This occurred at an average pull-out strength of 373 pounds. This, again, was deemed acceptable because this loading was well above what would be seen in vivo.

So in summary, we performed three different series of fatigue testing with a total number of 15 joints. All 15 joints made it to ten million cycles without failure. In the static testing of the mandibular component condylar neck bent at an average loading of 576 pounds.

The pull through test on the fossa screws showed an average pull through strength of 80 pounds. The compression of the fossa flange showed that the fossa flange bends at an average of 83 pounds, and on the pull-out testing of the 2.7 millimeter screws, there's an average pull-out of 373 pounds.

DR. QUINN: Good morning. My name is Peter Quinn.

I'm the Chairman of Oral Surgery at University of Pennsylvania, and along with Doug Sinn I'd like to stand for a second.

We performed the majority of the surgeries in this study. Doug is the Chairman at the University of Texas Southwest in Dallas.

While I'm waiting for this to boot, I thought what we might do is look at some of the surgical aspects of this joint because I think it will help us to understand the development, and I know there are three surgeons on the panel, but for the non-surgeons, I thought it would be helpful to look at the unique aspects of this joint which actually have implications for how it was designed.

We began the design process in 1991 and enrolled the first patient in 1995. This is the prosthesis with the polyethylene fossa and cobalt chrome ramal component.

I would just like to point out at the beginning the reasons for pursuing this is that we feel strongly that a prosthetic joint does have advantages, and on the left they really are in terms of a quality improvement standpoint lack of donor site morbidity, reduced intraoperative time, a potential for decreased hospitalization, and immediate functional ability as opposed to grafts, autogenous grafts.

Also, you can maintain the occlusion or actually change it as you'll see, which is an opportunity you get with a prosthesis over an autogenous graft, the opportunity manipulate the design to discourage heterotopic bone formation, and again, the opportunity to correct occlusion.

These I think are extremely important because we still do a large number of autogenous rib grafts in children, and we believe that that is the procedure of choice in the skeletally immature patient.

In the skeletally mature patient with an acceptable indication, we think there should be a safe and efficacious stock prosthesis. We also believe firmly that in patients who are anatomically mutilated, who have undergone multiple operations where this stock prosthesis or any would not be appropriate, we use a CAD-CAM 3D construction by TMJ Concepts, which we also think is a very safe and effective prosthesis.

The relative contraindications for the alloplastic joint is allergy, and we'll see we've had two patients with nickel allergy where we have FDA approval to use titanium instead of cobalt chromium; chronic infection; skeletal immaturity, as I've mentioned; and any systemic disease that would increase the risk of infection.

Now, briefly, and I usually talk fast, but I'll talk faster today, I just wanted to show you the unique aspects because I do think after 22 years I have been humbled by this joint. It is a unique joint in its mechanics and also in terms of its approach because when I watch my orthopedic colleagues, they're able to make bigger incisions and see the entire construct.

We are always working in a tunnel between the facial nerve, and the other issue we have to deal with is the vasculature. So this is a standard procedure with a modified face lift or rhytidectomy incision to place the fossa in a posterior mandibular incisions, to place the ramal component.

I'm going to go through these just because I do think after Shawn's presentation we can understand the design based on the surgical technique, and once the preauricular and posterior mandibular incisions are made, I think the first thing you will note is the thickness of the fossa which is dictated by the minimal thickness that you can have in polyethylene to have sufficient wear resistance.

That does push condylion, which is the point of rotation. The normal condyle is higher, and you'll see in some radiographs that it just pushed that point out.

It also means that we remove more bone in the superior

surface than other joints. This is a standard condylectomy osteotomy cut. This actually is still performed for ankylosis where the condyle is just removed and nothing is replaced, which we don't think is indicated.

In this joint we use a two-step osteotomy where we remove the upper part of the condyle. Then in the space created by that cut, we push the ramus up, which is a safer way of removing further bone, to accommodate the fossa, and in multiply operated patients, we remove the coronoid because it gives them a greater opening.

Special instruments have been designed, and thee are condylar retractors, and what these are protecting against is the internal maxillary artery that runs medial to the neck of the condyle, and these are designed to avoid any damage to that.

Here's a standard cut through an ankylose joint, and you can see we don't like to instrument more inferior here because of the facial nerve that's coming through the junction of the auricle. So what we do is remove the upper portion.

The lower incision has been made. You can just see the hint of it here, for two reasons. If there's any bleeding, we can control it from the lower incision by ligating branches of the carotid.

And, secondly, once this portion is moved, we literally move the ramus up and remove what other additional bone may have to be removed to fit the fossa.

As Shawn said, this is an ultra high molecular weight polyethylene in the fossa. It was designed to have maximum mating between the condyle and the fossa. Remember this is a ginglimal, arthrodial joint that both rotates and translates. Prosthetic joints only rotate because we are going to remove the lateral pterygoid head.

I'm going to talk about the PMMA because it was used early in the study. We have not place PMMA cement after 1998. What we did in the early cadaver studies when we designed the joint was found that over 70 percent of the variability in the human temporomandibular joint is in the articular eminence.

So this implant is designed to flatten the articular eminence, and there are specially designed burrs to do that, which flatten the articular eminence to give you tripod stability of the fossa implant.

And here is an articular eminence that has been flattened, and as you'll see, the burr was designed not only to take the eminence off, but to give you the radial curve of the implant itself.

This is a fossa and the condyle in position. In terms of timing, we actually place the fossa, and then go back and put the patient in fixation, and this is, again, what's unique to this joint as opposed to orthopedic joints.

Here's a picture of the fossa with the burr design, and this was one of the major reasons why we're able to discontinue the use of the cement because after the fit got better and better with time, we were using less than one cc of PMMA, and it did not seem to be appropriate to continue its use.

These are sizers, and this fossa is in three different sizes. What is uniform is the articulating surface. This doesn't change.

What does change is the number of preconstructed holes to give you options in the zygomatic arch.

Again, in the beginning of this study, we were approved to use PMMA only for void filling. Our original intent was to ultimately replace it, but we have stopped using it completely because it was designed in the beginning -- this is one of the first devices we used in the laboratory. You can see what the peg was used for in terms of retention. Other than that it has no role.

So once the fossa is placed in position we then put

the patient in fixation. This is work done in the Netherlands in 1993, which determined that if you move the point of rotation inferiorally -- and these are cadaver studies that we first did in 1992 -- there was some pseudo translation. The jaw is being opened on the right, and you can see there's almost a ramping, gliding effect of this prosthesis, which is not true translation which you can only get with a lateral pterygoid muscle.

In this slide you can see these are TMJ implants incorporated. This is a metal to metal joint that had to be removed because of metallosis and foreign body reaction, but what you see is when it's replaced with the Lorenz, that you've lowered the point of rotation. If you compare where a normal condyle and even this prosthetic condyle seats in an inferior/superior component.

The condylar component, again, is a cobalt chromium. It's secured with 2.7 millimeter screws. This is the narrow design, and we have both designs because we do see a patient population who on the average has over five surgeries, and some as many as 29 surgical procedures.

In those cases we did come up with a broader footplate here to give us more options to put screws because in some of these rami there are multiple screw holes. There's damage to the cortical

bone from previous rib graphs.

You can see an ankylose joint here that's been replaced with the standard design. This is the approach to place the lower component or the condylar component, and you can see we get complete visibility of the ramus, and we can place all of the screws through this lower incision.

The other aspect that Shawn mentioned is this Swan neck design, and this does differ from all of the -- some of the other prosthetic joints that have a right angle, a 90 degree bend at the condylar head, and that somewhat assumes that you can predict where the osteotomy cut will be, which is usually not the case.

This allows you to have some medial lateral change by moving this condylar up and down, and it allows you to change the medial lateral position somewhat by altering the bone at the superior edge of the ramus.

It's in contrast to some other joint prostheses that have been used. Briefly, this is the Kent-Vitek. This was Synthes. This is Delrin Timesh. This is Christensen I, with an acrylic head, and Christensen II, with an acrylic head. And you can see part of the difference is the angulation, and this mimics the angulation of the normal condyle at approximately 20 degrees.

So the mating is spherical. We made the condylar

head as large as possible to give us a greater surface area for the load distribution. These are the templates we use to determine what size condylar component we'll use.

And you can see here a patient who has had -- this patient actually had 16 operations. These are two failed rib graphs that you can see have detached completely from the ramus and are free floating, and this is the wider design because in these patients who have had multiple surgery, we sometimes wind up with poor quality cortical bone on the ramus.

The current available lengths of the prosthesis are 45, 50, and 55, and this is the standard design. What this allows you to do is if there's damage to cortical bone with a preoperative X-ray that you can determine where the inferior alveolar nerve is, you are able to place screws anterior and posterior to the nerve and find better cortical bone where it has been destroyed by previous surgery.

Again, after the fossa is placed, we place the patient into intermaxillary fixation because there is very little leeway in the placement of these joints. In my clinical experience, there's about 25 to 30 percent of the time we literally change the position of the condyle after checking the occlusion and the range of motion.

It's originally placed with two screws only, and if you remember, the other unique thing here is we are in and out of the mouth. We're in and out of from a sterile to a non-sterile field.

So we place the condylar prosthesis tentatively, check the range of motion, and then only secure it when we're happy with it. We have designed some special sterile mandibular manipulators that allow the surgeon to move the mandible and check the actual mechanics of the joint, but it clearly has to be checked before the final screws are placed in the condylar prosthesis.

This is a patient who is four months out. You can see these rhytidectomy incisions can be hidden rather well in the preauricular crease and in the post mandibular crease.

Lastly, just an example of a patient, the type of patient we see. This is a 28 year old male who had bilateral condylar fractures as a child, I would guess anywhere between seven and eight years of age, just given the retrognathia. He is completely fused. There's no oral opening at all.

He's had four operations. Most of them are gap arthroplasties, which is the standard way of just going in and cutting it, all of which refuses. And you can see he's completely fused to the base of the skull.

This is a case where even though we used a lot of custom joints, even this one, I think, would be difficult because it would be difficult to somewhat predict exactly where your surgery cuts would be because of the massive amount of bone here that is fusing him to the base of the skull.

The other thing we mentioned earlier is the ability -- and you only have this ability with bilateral prostheses. You can't do it with the unilateral prosthesis -- is to change the occlusion. Once the mandible is freed, if you're going to place bilateral joints, you can bring the mandible forwards or backwards, and you can change the preexisting occlusion, which I think is a major advantage of prosthetic joints.

And you can see here that we do remove large amounts of bone because we do have concern of heterotopic bone. When I discuss adverse events, you'll see our reasonable goal for entrance size of opening is approximately 30 to 33. Remember normal opening in an adult can be 45 to 53. We don't achieve that because these joints only rotate. They don't translate.

So that's what we think is a reasonable outcome. We have complications just briefly. I'll show you the two that I think are most vexing, but you'll see the numbers are more than acceptable -- is infection. This is a fistula that has developed.

The fossa had to be removed, and after a protracted course of IV antibiotics, we were able to reinsert one.

That's not always the case, as I'll show you later, and I think one of the most difficult problems we have is heterotopic bone, as the orthopedic surgeons do as well. This is a young African American female who has got horrific keloids, and I think that heterotopic bone and keloids are simply analogous genetic aberrations in soft tissue and bone.

But we placed a prosthesis in her, and you can see she has completely fused to the base of the skull. This is a very difficult problem.

Actually this patient has had a revision where we removed the prosthesis, removed the bone, and in this patient we've radiated her with 1,000 rads of radiation over five days, and she seems to be doing very well, maintaining an opening of about 26 millimeters at this time.

So that's a quick overview of the clinical application, and do you want me to start the other one?

And Mary Verstynen, whom I'd like to introduce, is the Director of Clinical Affairs of Biomet, who has also been my monitor and guiding light. We are going to kind of off and on give you the statistical results of the study.

MS. VERSTYNEN: The clinical investigation will be presented by Dr. Quinn and myself, and please note the handouts that you have. We have done an abbreviated form of this slide presentation in order to keep with the time frame required.

In 1994, an IDE was submitted to the FDA for a prospective multi-center clinical trial. It was designed to document patient improvement from baseline to postoperative visits. In other words, the patient was serve as their own control.

The patient population was purposely defined very broadly. There were very few exclusions, and the inclusions are listed on this slide with unilateral and bilateral cases being used.

There were multiple diagnoses that were included within the study protocol. One of the only exclusions or one of the few exclusions was the patients had to be skeletally mature, but most importantly, the patients had to be selected after nonsurgical treatment failure or previous implant failure.

A study design included collection of baseline data, operative data, and follow-up data. The follow-up data as listed ran from one month to three months or three years, with the three years being a study endpoint, and this was based on an FDA draft guidance document that was available at the time.

The primary efficacy assessments as defined in the protocol were jaw pain intensity, interference with eating, and MIO. The jaw pain intensity and interference with eating were collected on ten centimeter VAS scales which went from zero to ten with zero being either no pain or no interference with eating, and ten being worst case.

The MIO was collected in terms of millimeters. Additional efficacy assessments included occlusion and anterior open bite, cross bite, and wound healing.

Safety assessments were documented as adverse events, device related or otherwise, and in addition, radiographic assessments were collected at each of the follow-up time periods which are listed as follows.

The position of implants were compared to immediate post-op, and then additional X-ray findings.

We also defined patient and study success, which will follow on the next slide, and in addition, we identified primary efficacy endpoints and secondary efficacy endpoints.

The study was based on improvement from baseline to three years. So the primary efficacy endpoint was the difference between baseline and three years for pain, interference with eating, and MIO.

And then in addition, the secondary endpoints looked at the same pain interference with eating and MIO at baseline and then at each of the individual follow-ups.

In addition, we included as a secondary efficacy endpoint patient satisfaction, which also included a question of whether or not the patients would be willing to have the surgery again.

Patient success is defined as follows with patients having to meet both criteria to be a success. In order to be a success, they had to have no permanent joint removal in two of the following three assessments, which were the primary efficacy endpoints.

There had to be a one centimeter reduction in pain from baseline to three years and/or a one centimeter reduction in eating also at the same time frame, and an increase of MIO of ten percent once again from baseline to three years.

A study success was determined that if 60 percent of the patients met the success criteria, the study would be a success.

The statistical plan analyzed three different groups of which there were two cohort groups and the total study group which was comprised of 180 cases and 256 joints.

The first cohort group is the cohort unimputed group, which included 45 cases which actually had follow-up at the three-year time frame. The cohort imputed group included those 45 cases, plus imputed data from the closest follow-up time point to the three years but not past it.

So if a patient was seen at the one-year time point and wasn't seen at three years, we would input the values for that.

In addition, the statistical plan outlined that we would do T test analysis and repeated measures analysis for the primary and secondary endpoints, and we also would do subgroup covariate and multivariate analysis.

Dr. Quinn will take over from here now with the baseline findings and the following tables will show the cohort and the total groups to show how comparative these groups were.

DR. QUINN: And, again, I think it is a unique patient population. These are multiply operated patients. There are some unique characteristics that tend to be similar to other joint studies. So it wasn't that this study was different than other TMJ findings, but there is some unique characteristics of that patient group.

The mean age -- and, again, I'm going to try to point out the similarities in the total group and the cohort group --

was 40.2 and 37.8. The gender follows most TMJ studies, and I'm not sure anyone has a good explanation, but they are usually close to 90 percent female. There's mechanical reasons for that because of the differences in Type II collagen between men and women, and there are some biochemical discussions about estrogen receptors that may affect some of the issues, but this is clearly consistent with other studies.

The sidedness broke out relatively even between unilateral and bilateral. It was almost 50-50 in between right and left side.

The majority of the cases, as I've mentioned, they were done between Dr. Sinn and I, and in the cohort group, it broke out around the same percentages.

The baseline medical history, again, is somewhat similar for these group of patients, and again, as I mentioned before, these are humbling patients because the criteria for success that Mary mentioned, I think one of the reviewers said we had somewhat lenient criteria for success. I think it was based pretty much on our experience with these multiply operated patients. As you'll see, we far exceeded those criteria for success, as we'll see later on.

We used a Wilkes classification, which is named after

Clyde Wilkes, which actually just classifies according to pain, restriction in motion, and radiographic findings, and as you would suspect, the majority of these patients would fall into the higher Wilkes stages, which is consistent with these patients should exhaust all nonsurgical therapy, clearly, before ever proceeding to a total joint replacement.

This, again, I think tempers some of the results of the study, and they're very similar in the total and the cohort, the number of prior studies, and you can see they can range anywhere from zero to 29.

Zero would be a traumatic fracture where there's an irreparable fracture, and you would go right to a prosthesis. The 29 would be an unfortunate patient who underwent a lot of previous procedures.

The three major baseline characteristics we followed were, again, jaw pain intensity, interference with eating, and these two were on a visual analogue scale of zero to ten, where zero was the best and in pain, ten was the worth pain imaginable, and on the diet scale ten was liquids only. And the maximal interincisal opening, these are baseline findings between total and cohort, which are relatively similar, but they started around 19 to 20.

And, again, as we mentioned, we feel it's a reasonable goal to get probably 30 to 33 millimeter opening in the multiply operated patient.

The diagnoses are multiple because obviously these don't add up to 100, but if we look at the two most common, they are osteoarthritis and ankylosis, and then we had a separate traumatic arthritis when there was an identifiable event that began these symptoms.

In cement usage, as we mentioned early on, when we were using PMMA cement, of the total cases 38 were cemented and 142 are uncemented, and the last cemented case was 1998.

In the mandibular component, as we discussed the different designs, the narrow design, we've used 197. The standard, which is the broader that gives you just more options for screw placement, and in two patients who had documented nickel sensitivity, and these patients are actually tested with nickel patch testing by a dermatologist prior, and then in both cases we got FDA approval to make the mandibular component out of titanium. As you recall, the screws are the titanium alloy.

This is the follow-up. If you look at the landmarks of follow-up, and Mary is going to go through the statistics from this point on, and then I'm going to discuss the adverse events

tat the end.

MS. VERSTYNEN: Patient accountability. This shows once again while the study went from one month to three-year follow-up, I also did include the four and five-year follow-up because we did make an effort to follow the patients past the three-year study time point.

As you can see, the bottom line and the most important thing on this slide is the percent follow-up from the one month to the three years, and at all time points we were at greater than 80 percent.

The only loss to follow-ups that were calculated on this slide were deaths and total joint removals, but obviously people do not return for visits. People move; people are lost. So that accounts for why we would have some patients theoretically due at one month of 180 when we actually saw 170 patients.

I mean, the patients schedule, and they don't come back. And Dr. Quinn and Dr. Sinn can probably talk a lot more in detail why patients don't come back for follow-up.

The clinical findings, the primary effort to see endpoints in both T tests and repeated measures analysis. They showed a significant change from baseline to three years, and remember this study was designed to show improvement.

This slide shows perfectly how well the three groups that were analyzed compare, and if you look to see, they follow the exact same pattern from baseline to three years throughout the course of the study, with the baseline mean being at eight and the error bars are put in for just the standard deviation only just so it wouldn't complicate the slide.

But you can definitely see even at the one month time frame there was a tremendous amount of improvement in jaw pain, continued down at three months, and pretty much plateaued from the six-month to the three-year time frame.

This was also seen very similar on the interference with eating. Remember these were all in the ten centimeter VAS scale where, once again baseline mean for all three groups was approximately eight centimeters, dropped drastically at one month, continued going down at three months, a little decrease still at six months, and then pretty much plateaued out to three years, which pretty much seemed to be somewhat predictive then.

By the three and the six month mark, the patients had pretty much plateaued to what they were at the end of the study.

The same thing for the MIO. They started off with approximately a 19 millimeter opening and went up drastically at one month and at three months and was continuing up, and this pretty

much looked like it plateaued then out to the three-year mark.

So you can definitely see that there was a tremendous amount of improvement seen in the primary efficacy endpoints.

Also, to show this even in another visual way, once again, this was the baseline reading. We wanted to see the difference between baseline and each of the time frames, and this slide actually incorporates both primary and the secondary efficacy endpoints.

We can drastically see the difference between baseline and three years, which was the primary endpoint, and then each of the secondary endpoints then are shown at the one month and all of the follow-ups.

And you can definitely see there was a tremendous amount of significance in improvement for jaw pain, and you can also see the exact same thing then for the interference with eating and the same thing for the MIO.

Once again, this was just to visually show you what the baseline reading was and then to actually show the improvement over time.

Secondary efficacy endpoints also included the degree of patient satisfaction. Ninety-three percent or more of the patients were satisfied or better at all time frames, and that

includes out to the six years, and for the hindsight question, whether patient would choose to have a surgery, 91 percent or more said yes at all of the time frames.

This slide is just to show you that with the additional efficacy data that was collected for collusion, anterior open bit, and cross bite, there was also an improvement seen from baseline to three hears in these three assessments.

I will hand it over now to Dr. Quinn to complete the clinical presentation, and he will start off with safety findings.

DR. QUINN: Thanks.

As we mentioned, we reported adverse events. You'll see, I think, we over reported them. We're very conservative with that.

There weren't any mechanical failures. There were permanent device loss, and we'll go over all of them. And the permanent device removals occurred in 11 cases and 12 joints.

Now, we defined "permanent" that it was removed. In three of these the fossas have been replaced. One of them is as long as two and a half years later, but we are still listing these as permanent device removals because the other definition we used was same day revision.

I don't want it to be confusing, but same day revision is where we went in, removed a prosthesis, for example, for heterotopic bone, removed the heterotopic bone and replaced the prosthesis. And that occurred in five joints, four cases where we had to remove the heterotopic bone, and in one case where there was a dislocation of the condyle, and we went in and replaced it with a 50 millimeter to a 45 millimeter to reseat it.

This is the total number of adverse events which are not requiring device removal, and again, I do think that we made an effort to over report. I'll give you some examples of these.

Excision of tissue included both removal of heterotopic bone and also removal of incisional neuroma because a lot of these patients especially who have had multiple incisions have incisional pain that can occur in any type of incision, and some of them postoperatively were taken back to remove the scar in an attempt to remove an incisional neuroma.

We reported any time when there was a motor vehicle accident even if there was no direct facial trauma because we did see that it did correlate with an increase in symptoms even if there was no direct maxillofacial trauma.

Coronoidectomy, I think there's some experiential

wisdom here. In the beginning of the case, we probably did not remove coronoids as much. We were recommending in the multiply operated patient at the time of the original surgery that the coronoids were removed.

We did have to go back and remove coronoids. That's from an intraoral approach, and it does avoid contaminating the implant.

Again, these are all adverse events that did not require a device removal, and as I mentioned, we had no mechanical failures. This does come out to a 30 percent AE incidence, and 55 patients at the 180 cases, but it was six cases or 3.3 percent that had AEs that were device related. And, again, as I mentioned before, the number that had the permanent removals.

Given the patient population where I think the term "reasonable expectations" comes in, these patients do have, especially in the multiply operated patient, preexisting conditions, nerve pain secondary to multiple surgery which will not be addressed by a prosthesis, and some of these patients are chronic pain patients as well.

Looking at the surgical site, most of the wounds healed within the first three months postoperatively. The ones where we had wound infections I showed an example of where we had

device removal.

Radiographic assessment was done at all of the landmarks, and we used the baseline of the day after surgery where a PA cephalometric X-ray was taken, a lateral cephalometric X-ray, a Panorex, and they were compared at the other landmarks for change in position of the fossa or the condyle.

Most of the radiographic changes were associated with the heterotopic bone or in the joints that were removed.

There was a subgroup analysis done for a covariate analysis and multivariate analysis, and all the detail of that is in your handout.

What did occur from that analysis was that there were some statistically significant differences in the variable analysis, but none of them were clinically significant.

If you looked at groups where one has a three centimeter improvement in opening, the other subgroup had a four centimeter. They were, again, statistically significant, but all of the groups did well enough, and so they weren't clinically significant.

In summary then we had a success rate by the definition that we went over in the beginning of the presentation in the cohort on imputed group, the 97.8 percent, and the cohort

imputed group of 94.9, and then the total study group of 95.1, and we had greater than 60 percent of the cases met the patient success criteria, and as we said, those criteria were a centimeter improvement in pain scale, a centimeter improvement in diet scale, and ten percent improvement in the MIO.

The study conclusions is that we feel this is a safe and efficacious implant. There was a significant improvement with a significant P value seen in the primary and secondary efficacy endpoints.

Patient satisfaction was what we reported, approximately 91 percent, and the rate of AEs even including device removal was an acceptable rate considering the patient population, and we had no unanticipated adverse events.

In summary, we think this prospective study has shown that the Water Lorenz total TMJ replacement system is safe and effective for the variety of diagnoses that we've shown.

Thank you.

CHAIRMAN HEFFEZ: Thank you very much.

I would like now to proceed to any questions that the panel may have. Any panel member who wishes to ask a question, please signal to me and identify you name prior to the question.

DR. PATTERS: Mark Patters.

A question for Dr. Quinn. Could you discuss the patients lost to follow-up? Because there's always a concern that that represents a population that's dissatisfied rather than that is consistent with the total population.

DR. QUINN: I'll separate the amount of patients who are lost to follow-up. There were three deaths in the study, and the three deaths were one was a patient who had a temporal lobe tumor who died of a recurrent brain tumor.

The second patient died from a fulminant hepatitic reaction to Toradol three weeks after surgery.

And the third patient died from complications of back surgery. So there were three loss to follow-up from death.

Of the other patients that were lose to follow-up, the majority of the problem is distance. We do a zip code analysis at the University of Pennsylvania, and based on this study I now have the widest zip code analysis patient referral base. So most of the patients, it's distance.

And my impression is that if they're doing well they don't want to get on a plane and fly back from Oregon for a 20 minute appointment in Philadelphia. That is a problem.

So my impression is that the percent follow-up, given this patient population, is laudable, but you're right. It is

a concern, and the problem is coaxing patients back in. We have no problem getting patients back in who have complaints.

DR. BURTON: Richard Burton.

This question, Dr. Quinn, deals with your indications and your patient population. The first one is that one of your indications and one of your exclusion criteria was that they would be skeletally mature.

But then looking at the demographics, that shows at least one male that was 12, and then a 13 year old female, and most of us would obviously not consider those to be skeletally mature. So I guess my question is why. There was no indication why they were included.

DR. QUINN: The 13 year old female was by hand wrist filmed, finished skeletal growth.

DR. BURTON: Okay.

DR. QUINN: And she's the patient I showed, the young Afro-American female with the keloids and the ankylosis.

DR. BURTON: Okay.

DR. QUINN: That is her. The 12 year old patient, the patient of Dr. Sinn's -- and, Doug, if you want to comment -- that patient was approved by the FDA as an exclusions even given his age.

DR. BURTON: Well, they were an exception to that.

Also, what is your intent in the section? You talk about one of the indications is developmental abnormalities. That's sort of a broad term, but what you really intend by that statement.

DR. QUINN: Development abnormalities, we may have a congenital absence of the whole -- rami are kind of like hemifacial microsomia or Golden-Harr syndrome.

Obviously, the procedure of choice in a developmental abnormality prior to skeletal maturation in our hands is still a costocondyle graft, but developmental abnormalities after skeletal maturation could be addressed with the prosthesis.

DR. BURTON: And lastly you had some individuals who were -- at least a couple that were Wilkes Class I and then a couple of IIs and IIIs. What were the other co-morbidities that usually would indicate that they would be included? Was that a fracture patient or something along that line?

DR. QUINN: Either fractures or a tumor where the amount of bone removed in the tumor excision would require either a prosthesis or an autogenous joint.

DR. BURTON: Okay. Thank you.

DR. SUZUKI: Jon Suzuki.

This is a question for Dr. Quinn.

Apparently the condylectomies that are required to place this device are somewhat radical, and an additional part of the mandible is taken off. Given the morbidity, what options does a surgeon have for reconstitution or replacement of it should this fail?

DR. QUINN: That's a good question. You do have to remove more of the condyle approximately three millimeters below the sigmoid notch to accommodate the thickness of the glenoid fossa. That is an irreversible step, as you point out.

And I'll phrase it in two questions. You always have the option in a failed prosthesis to go back to an autogenous graft. I think there's some complications there because the more these patients are operated on, the more scarred the bed is and the more complications you will get with autogenous grafts.

The other option, and I should mention this, is that this is a stock prosthesis, and it comes in three different sizes, and humans always don't come in three different sizes. You always have the option at the time of surgery, the stock prosthesis once the surgeon is in the joint. It doesn't fit, is inappropriate. you stop the procedure, put the patient in IMF. Do a 3D CT scan in the hospital, and you can proceed with a well designed custom

joint like the TMJ Concepts.

And we do encourage surgeons that that is an option if they run into anatomical problems. Is that addressing your question?

DR. SUZUKI: Yes. Thank you.

DR. COCHRAN: David Cochran.

I had a question about the timing of your adverse events. When those occurred, it looked like from some of the information they occurred around the six month time point. Would you elaborate on that a little bit?

DR. QUINN: The timing of when the adverse events occurred?

DR. COCHRAN: Yes.

DR. QUINN: I think they occurred throughout the entire study. Maybe I'm misinterpreting the question.

DR. COCHRAN: Yeah, it looked like just from what was listed in the material we had, it looked like they were occurring from four to ten months. The main ones were listed. I think there was one lost later on, but normally four to ten months seemed to be when most of the adverse events occurred.

DR. QUINN: Well, for the major adverse events, infection and heterotopic bone, that would be the time frame it

would occur in. I'd ask either Mary or Joe Canner if you want to discuss the statistics. Maybe I can't answer the question as well.

MS. VERSTYNEN: Yeah. Mary Verstynen.

I believe that the adverse events occurred throughout the study, but I guess if you go back and look and remember the patient accountability, the majority of whole joint revisions were done between the six month and the one and a half year time point. It seemed to be at that point is when the patients went back for the total joint.

So I don't know. Does that answer it somewhat?

But literally the rest of the adverse events occurred throughout the study.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: Diane Rekow.

I have a question for Dr. Quinn, and then I have another question for Shawn, please.

Dr. Quinn, can you talk about and have you done any correlation -- let me start again.

My impression as I read the materials was that you used the bone cement with a post early on, and then you started removing the post and not using the cement. Then that evolved

into a new design. Is there any correlation between the adverse effects and the use of cement or non-use of cement and the design of the fossa?

DR. QUINN: I believe that was one of the subgroup analysis, and I don't think there was a statistical significant difference because as you mentioned, we stopped in 1998.

Of the patients who were out -- Mary, can you help me with the numbers? -- of the patients who were out three years, of the breakdown, I think it's 38 and six.

MS. VERSTYNEN: Well, there were 38 cemented cases, and they were obviously done early on in the study. So there were 31 of Dr. Quinn's and there were seven of Dr. Sinn's. So these, this grouping of patients, were their first patients that were enrolled into the study.

Does that answer it or do you want --

DR. REKOW: And there's nothing different?

MS. VERSTYNEN: And the thing is I guess you could kind of go back and look at the key numbers. I mean, with the listing of adverse events, they probably fell within the first 40 key numbers. I don't know that those cases had more adverse events than the rest of the patients.

DR. REKOW: Have you -- have you --

MS. VERSTYNEN: But we haven't actually looked at the 38 and correlated it back to the numbers of adverse events.

DR. REKOW: Okay. That was really my question.

MS. VERSTYNEN: Actually it was a good point. The 38 cases were all in the cohort group, but once again, we didn't list adverse events by cohort. We just listed them by the total of 180 cases.

DR. REKOW: Okay, and then, Shawn Roman, you provided some nice information about averages for your mechanical testing, but I didn't see any ranges or standard deviations. Can you give us some sense of how closely the five joints performed relative to each other?

MR. ROMAN: With respect to the?

DR. REKOW: Well, the fatigue testing and your screw pull-out tests and those sorts of things. The averages are wonderful, but you could have interesting results with nice averages.

MR. ROMAN: Right. I don't have those numbers off the top of my head, but I can get those from the test reports if you'd like me to do that.

DR. REKOW: I think at some point it would be useful to see those.

MR. ROMAN: Okay.

DR. REKOW: Thanks.

CHAIRMAN HEFFEZ: We can entertain another question.

MR. ROMAN: Just pointing out the fact that on fatigue testing there is no variability. The fatigue testing just stops at the --

DR. REKOW: Right, right, but for the bending tests and for the pull-out tests?

MR. ROMAN: Sure. How would you like to work this? I can get the numbers and then come back to the podium and answer that question for you?

CHAIRMAN HEFFEZ: Yes.

MR. ROMAN: Okay.

CHAIRMAN HEFFEZ: We'll proceed.

Ms. Helms.

MS. HELMS: Thank you.

Elizabeth Helms.

I have several questions around the function of the mandible after implantation with the screws. The screws loosen up. Do you have to go back in? Has there been a change in the body of these patients?

If you could describe how many patients have had

screws that have loosened up. What happens to the body if any of this is reabsorbed?

And for the nickel testing, do you do any type of testing for nickel allergies prior to implantation?

DR. QUINN: Maybe I'll answer them in reverse.

MS. HELMS: All right.

DR. QUINN: Nickel testing, if a patient tells us they have nickel sensitivity, and most patients who have nickel sensitivity, it's a jewelry issue because of the preponderance of nickel in jewelry, and we have small samples of the materials.

The polyethylene and the cobalt chrome from the company that we send to a dermatologist, have the patient seen by the dermatologist, and they're patch tested. I'm not sure there's any other way other than taking a history and doing a patch test.

If there's a reaction to the patch testing, then we have gotten permission to use titanium in the ramal component as well as the screws.

We haven't had any screws loose in there. I have had screws loose in implants that we've used in the past. Fortunately we've had no device failures.

The question about wear, I think there is wear in

all prosthetic implants. The implants that we have gone back into for infection or for heterotopic mode, we've taken tissue samples. One of the samples came out with a foreign body reaction. When it was put under polarized light, the official diagnosis that it was corn starch because it polarizes in a very particular way was probably from a glove.

So we haven't seen any evidence of foreign body reaction yet.

CHAIRMAN HEFFEZ: Dr. Hewlett, you had a question?

DR. HEWLETT: Yes. Edmond Hewlett for Dr. Quinn.

I noticed in your statistical analysis or actually in your demographic data collection that patient ethnicity was not one of your demographic variables.

A two-part question: have you considered at any point or make a specific decision not to include that?

And the second part is that did you nonetheless based on just your empirical experience in the study notice any propensity for specific adverse effects, such as heterotopic bone or ankylosis with respect to any particular ethnic groups?

DR. QUINN: Well, the numbers wouldn't be high enough. Anecdotally, I think in my patient population and only in the females, there were three African American females. Only

one of them have this serious heterotopic bone. I do think there is a higher propensity in African Americans in general for keloids. I don't know whether that translates into heterotopic bone.

My experience with heterotopic bone is it gets worse as the number of operations gets. I think the actual surgery in and of itself is the trigger for further and further scarring in heterotopic bone, but I'm not sure I'm an expert in it beyond that.

As you said, we did not follow up density. We followed gender alone, and gender is the striking differential in all of these TMJ studies, as you well know.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

For Dr. Quinn, I seem to remember reading that ten sites were okayed to participate in this study. Yet almost all of the surgeries are done by you and Dr. Sinn. Can you shed some light on why predominantly just you and not more sites?

DR. QUINN: One of it is a temporal issue. Since we started this process in 1992, I think we were somewhat geared up for that patient population.

The other is this is exclusive what I do. I only do TMJ surgery. My five partners won't do any of it, and we have a large center.

We also have, as you know, a TMJ clinic that sees a huge number, and our surgery rate is about six percent out of 100. So we tend to draw from a larger population.

Dr. Sinn is in a similar position at Southwest Texas. He came out in 1998. I think the other investigators, I think there's two sides to that. There are investigators who have given us the impression that they have lots of patients and they didn't materialize, and they came in later in the course, as in the last year or so we have been holding off and not doing more IDEs and IRBs because they're so labor intensive to do for somebody who may do two or three surgeries.

DR. BERTRAND: I understand. The second question, there seems to be an evolutionary process in the design of the standard mandibular component. Do you anticipate any more design changes for the product?

DR. QUINN: No. And it is. It's experiential wisdom. I think as you go on and you run into joints where you don't have adequate bone, where a bigger footplate would give you more options, that clearly was one.

The other one was the medial lateral issue because, again, this is a stock prosthesis, and it does take some experience on the surgeon's hands to fit this. But if the fossa is fit first

and there is some variability between where the condyle sits under that fossa, you have some leeway in terms of encountering bone, but we wanted to have the option to have the same offset in a lateral direction as the medial direction, if you did get one of them where you could.

It's relatively easy if the prosthesis is too lateral to do bony contouring to get it in. If it starts off to medial, you would have to do a lot of shimming with bone, which we don't want to do. So we made the other offset size.

I don't anticipate any more at this time, but I'm not sure I could sign an affidavit to that.

DR. BERTRAND: I understand. There seems also to be an experience level with how quickly and efficaciously you can do this surgery. Do you anticipate, with all of your experience and somebody new, anticipating using these devices having some type of mentorship program?

DR. QUINN: Clearly. I think without training and education this is very experience based. In fact, I think one of the things that did occur during the course of the surgery is it's a much faster procedure when you have all of the instruments that are designed specifically for it, the burs, the retractors. Our average time per side now is about two hours and 20 minutes.

In the beginning it was over four.

DR. BERTRAND: Thank you.

DR. BURTON: Richard Burton, again, for Dr. Quinn.

I'd like to continue with what Dr. Bertrand asked because I have concerns which you explained regarding the site and the question of site bias, but my concern looking through your surgeon materials is the fact that they're very good, but again don't obviously convey some of the complexity of this.

And whether or not you looked at whether your complication rate -- and when I went through the adverse events, it appeared that there was not a -- that they spread throughout the study, but there were certainly, it seemed, a slightly higher rate. Did you look at that earlier in the early patient groups?

And again, whether there was a learning curve, obviously you said your own surgical time improved, which would be a normal expectation, but again, how you may address the surgeon education issue when this was released.

Because, again, you know, currently virtually all of these have been done by yourself and Dr. Sinn, and again, both of you are, I think, well known and well experienced, but when his product is released and given out to hands with much less experience, and again, none with this particular product and how

you intend to address that.

And then one other question that sort of goes in with that if you've addressed many times that one of the most common problems you had was heterotrophic bone formation, again, in multiply operated joints. You made a comment earlier about the use of radiation in one of the patients.

Are you advocating that, and if so, how many patients did -- I didn't see anything where it said how many patients had received radiation in conjunction with their overall treatment.

DR. QUINN: Okay. Well, the only one patient received it, and it was actually three weeks ago after this data was closed.

I only have experience with three patients, and our experience is really drawn from the orthopedic literature because there isn't a lot in our literature how you deal with heterotopic bone, except for EDTA chelating agents which don't seem to be very effective, and indomethacin, which we have also tried.

A dose of 100 rads, given 200 rads per day, seems to be efficacious, but our n is too small for me to make any statement.

To go to your original statement about adverse events, I do think there are some correlates that, in general, in the maxillofacial literature, you can look at infection rates,

and they do correlate in general in orthognathic surgery, where it is published more, the longer that site is open, the higher the infection rate. I think there is some correlation to time of surgery.

It wasn't part of our analysis, but I do think if you take a two-hour operation and take ten hours to do it, you're probably going to increase your rate of infection. That's anecdotal. I have no data to support that.

To the training issue, I couldn't agree with you more. I think if there is any silver lining to the Proplast debacle, that as you well know, the majority of oral maxillofacial surgeons in practice have decided TMJ surgery is not something they're wildly enthusiastic about. I somewhat hope it stays that way.

These are done at centers by people who do at least a modicum of surgery because experience is part of it.

In terms of the training, currently the plan is that Dr. Sinn or I would do a surgery with anyone contemplating doing this, and they would have to take a formal course that goes over all of the testing, the designs, the biomechanical and surgical technique.

We've produced a video that is in preparation. Beyond that I would be open to suggestions because I do think it's

an important point.

DR. BURTON: Thank you.

DR. ANSETH: I had a question for Mr. Roman.

CHAIRMAN HEFFEZ: This is Kristi Anseth.

DR. ANSETH: My name is Kristi Anseth.

And my question relates to some of the wear properties of the components that you were testing, and I was wondering if you could comment more specifically on that.

And then also, with some of the changes in using the cement and noncemented, if you could comment on the differences that might exist both in fatigue and wear.

MR. ROMAN: Okay. The materials used for both the fossa component and the mandibular component are materials that we've had a wide range of experience with previous to this design in orthopedic applications.

The wear characteristics were looked at on all of the fatigue testing. The articular surfaces of the fossa components were looked at, and there was no sign of wear after the ten million cycles in the fatigue testing.

Does that answer your first question?

And the second question, could you repeat?

DR. ANSETH: So you also presented data on even the

cemented version of the fossa.

MR. ROMAN: Right.

DR. ANSETH: And I was curious what you think of differences when you have no cement.

MR. ROMAN: Okay. We're actually trying to -- well, the cement that -- first of all, the bone cement was never intended to be used as a means for fixating the fossa component. It was just meant to fill voids between the fossa component and the glenoid fossa component. The sole means of fixation would be the fossa screws.

But we are currently doing some fatigue testing to look at the difference between the fossa components that had the post manually removed as compared to fossa components that were machined without the post, and in both of those cases, we're redoing that fatigue testing without using bone cement because that is how they would be implanted.

And we're testing five devices. Four of the devices are complete now, and they have all made it out to ten million cycles with no failures of the devices.

DR. REKOW: Can I ask a follow-up?

Diane Rekow. Can I ask a follow-up question?

When you're doing that fatigue testing, what do you

have as your supporting system under the fossa? Does it have a modulus that's similar to the bone or is it a steel or you know?

MR. ROMAN: Yeah, it's aluminum. So it would be stiffer than the bone. That would be in vivo.

DR. REKOW: Okay.

MR. ROMAN: Did you want me to follow up now with the question I was asked earlier on the standard deviations or do you want to --

CHAIRMAN HEFFEZ: Sure, yes. Go ahead.

MR. ROMAN: I was able to find the standard deviations on two of the four tests that weren't the T testing. On the fossa screw pull-through testing, there was a standard deviation -- there was an average of 79.8 pounds with a standard deviation of 2.5 pounds.

On the pull-out strength of the 2.7 millimeter self-tapping screws, it was an average of 373 pounds with a standard deviation of 68.8 pounds, and it's a slightly larger standard deviation that was discussed, and it's probably the result of using bovine cortical bone for the testing.

There was a concern over the standard deviation there because the loading was so high, and the other two tests that were performed, the static testing of the mandibular component and the

static testing of the fossa component, there were no standard deviations listed in the old test reports.

DR. REKOW: Do you have the ranges?

MR. ROMAN: Actually there's -- that data is not listed in the testing report. I think that the reason for that was because of the mode of failure that was seen. It was anticipated that the mandibular component would fracture at the flange. Actually the mode of failure occurred in two different stages with the mandibular component.

The first stage actually involved splitting of the bone, the tibial bone from the first screw up to the top surface of the bone, and then once that splitting occurred, then the bending of the mandibular component occurred.

So then on the fossa components, again, the anticipated mode of failure was fracture of the fossa flange, but when the fossa flange bent with no breaking, that was deemed acceptable solely because they would have the support of the temporal bone in vivo.

So were those numbers that were reported then the minimums for the set that were tested or were they the average? Do you -- I know that this is probably old data, and you may not have the answers immediately available.

MR. ROMAN: I don't, but they are discussed as the average in the test reports.

DR. REKOW: Okay. Thanks.

MR. ROMAN: But as long as we're catching up on questions, we did have some additional information for adverse effects that can be answered by our contract statistician.

MR. CANNER: My name is Joe Canner. I'm a statistical consultant with Hogan & Hartson in Washington, and I have financial interest in Biomet or Lorenz.

There was a question asked about adverse events after cement or noncement, and we did do that analysis, but I would strongly encourage caution with respect to the interpretation of it, although the results are fine. There was no statistically differences.

But any time those kinds of issues come up, keep in mind as was mentioned that the cemented cases were the first 38 cases and the noncemented were following that. So any patient selection issues, any learning curve issues will by nature complicate that analysis.

It does appear that, as was mentioned before, most of the removals -- and I'm sorry. I meant to say that I'm talking specifically about removals here because those are the adverse

events that probably are most relevant to the device. Most of them do appear to occur in the first 12 months and even in the noncemented cases, all of the removals were in the first 12 months, and even though there were a number of patients who were in that group who were followed out to two and three years.

So to recap, there was no statistically significant difference between cemented and noncemented cases in the rate of removal, but again, it would be difficult to make too much of that one way or the other because of changes over time and patient population and in surgeon experience.

CHAIRMAN HEFFEZ: Dr. Li.

DR. LI: Steve Li, either for Dr. Quinn or Mr. Roman.

I'd like to revisit the polyethylene wear issue. As you've mentioned the TMJ is kind of a corollary to the total hip and total knee system, and in this case it's a more conforming joint, so more similar to a total hip than a total knee, and yet your stresses are about two to three times that of a total hip.

So my question is: do you see signs of polyethylene wear either in radiographs or on your explants or in tissue analysis? And if you don't, why would that be?

DR. QUINN: I'll ask Shawn to answer some of the general questions about polyethylene wear because I'm not the

expert, but I think if you -- first of all, there's on real consensus as what are the stresses place on not only the prosthetic joint, but on the human joint.

You could start an argument as to what is the pounds per square inch under normal mastication. We used 145 pounds as the upper limit, which I think is a good estimate, but in this patient population in the multiply operated joints, there are studies that have viewed something as crude as a dynometer in multiply operated. Their masticatory forces are much less.

So I think although by definition this is a patient population who has already had multiple procedures, I wouldn't expect that they could even achieve the normal range of stresses.

The other is I'm not sure I correlate directly to a conforming hip joint where there's confluence because there is some aberrant motion in this joint that is not directly related to a hip.

DR. LI: But that would tend to increase the wear though.

MR. ROMAN: Right.

DR. LI: So my question is: do you see clinical signs of wear, either radiographically in the analysis of removed components or in surrounding tissues when you've gone in to do

procedures?

DR. QUINN: Excuse me. Radiographically we haven't. Of the joints I opened for other reasons, heterotopic bone and infection, when we did tissue samples, the only foreign body, as I mentioned, was what they came back and said was more likely to be corn starch and not polymeric debris. So --

DR. LI: Were those just -- I'm sorry -- were those just optical micrographs, with your eyes? It wasn't electron microscopes?

DR. QUINN: These were histologic EMN and then they were under polarized, but looking for foreign bodies.

DR. LI: Right. So typically in the larger joints the particles that form osteolysis are below the levels of visible observation. So if you can actually see it with your eyes, they're too big to cause osteolysis. So unless you do some tissue analysis to look for these submicron particles, there could be millions in there, and you'll never see them just by looking with a histological sample.

So have you looked at anything other than histological samples?

DR. QUINN: No, we haven't, and I'll ask Shawn if we have data on the wear of this particular high molecular

polyethylene, ArCom, which I think there is statistics on or Ken Beres might be able to answer that for us.

DR. BERES: I'm Ken Beres from Biomet.

I have a little bit more experience in the orthopedic realm. This joint is a cross between a total hip and a total knee. There is rotation of the joint similar to a total hip.

However, as Dr. Quinn said, there's also some translation, which would, again, move more towards a knee when you do have some sliding motion as well.

We thought about wear testing. We don't have a good wear simulator for a TMJ. So we couldn't do actual wear testing. There was no wear noted in a fatigue test and no clinical signs of wear noted.

I don't have the data here. We could do the stress analysis, the surface stress analysis on the polyethylene. We could do that easily. I don't think we have that data today.

DR. LI: Well, the stress really isn't that important because a total hip is about a quarter, 15 percent to 25 percent of the yield strength of the polyethylene, well below what you reported for your Fugi film, but even at ten percent of the yield stress, the rate of wear on total hip is more than enough to cause the osteolysis over a five to seven-year period.

So even if the stresses were half of what you said, that would still put you with a high enough stress to cause significant polyethylene wear.

So I think a more accurate contact stress would be useful, but it doesn't get you away from the wear question.

DR. BERES: Well, you know, wear is a very good question. We're trying to avoid the question. I don't know. Besides the clinical data, I don't know we could do simulator testing. I'm not sure how we do that right now because the fixtures and the machines are just not available.

DR. LI: In your laboratory test, I would not guess looking at the schematic of the fatigue test that that actually would be a very good wear test, but you said you looked at the components and saw no wear. So is that just a visual "I see now wear" or did you actually weigh samples before and after or do something quantitative?

DR. BERES: No. No, there was no quantitative or no -- it was just simply visual.

DR. LI: Okay. Thank you.

DR. BERES: Now, on the other side, you mentioned the polyethylene is the ArCom polyethylene, which I believe in orthopedics is one of the more well known and gold standard, if

you will. So we're using the same processing and all as with all the others.

DR. LI: Actually as you raise the issue, my understanding is ArCom actually can refer to several different products. For instance, I believe you have a product that you take the powder and you compression mold it into a bar, and then you machine the bar, and then you sterilize that in argon and call that ArCom.

There's also another product that you make where you take the powder and directly mold it into the final form with no machining and also call that ArCom, and they also may or may not use the same base polyethylene.

So when you say ArCom in this case, exactly what do you mean? And would it make a difference if you used one of the other versions of ArCom?

DR. BERES: ArCom, Ar stands for argon packaged. It's packaged in an argon package. Air is removed to reduce the amount of oxidation of the polyethylene while it's on the shelf. So we remove all of the oxygen from the package, replace it with argon, and it's vacuum sealed.

Com refers to compression molded. So the polyethylene we use is compression molded. We either compression

mold our bar stock, which is a unique method where we mold a bar. It's molded. Most of the other processes for making bar stock is an extrusion process, where it's an extrusion process to make a bar.

We compression mold the bar. So we compression mold the part. The part just happens to look like a bar, and then if the component is complicated enough, it has to be machined, but the starting material is power. It's compression molded into a particular generic shape, and then machined further to get the intricacies.

The other method of producing a part if the part is processable in a mold, you can directly mold the powder, put it into a mold, and mold the part as a finished component, but that requires that the part be somewhat generic enough that you don't have all of these intricacies that you just cannot mold.

DR. LI: Okay. Just one last, quick, detailed question. On your laboratory testing were the parts sterilized or not sterilized?

DR. BERES: I don't believe that's mentioned in the test reports.

DR. LI: So were they sterilized or not?

DR. BERES: I don't know the answer to that.

DR. LI: Because that could make a difference, particularly in your fatigue testing.

DR. BERES: We could go back to the original test reports.

DR. LI: Thank you.

CHAIRMAN HEFFEZ: I have a related question that perhaps Mr. Roman or Dr. Quinn could jointly answer. It's regarding the mating of the surfaces.

At the time of surgery you do your best effort to mate the surfaces, but clearly due to the access, sometimes it's difficult from a three dimensional point of view to mate them the way you'd really like.

So Part A of the question is have you had significant problems or not and how you have addressed them, and Part B of the question is was all of the fatigue stressing was done with them mated perfectly. Was any fatigue testing done with them mated incorrectly?

DR. QUINN: Okay. I'll answer the first part and Shawn will answer the second.

I think you're right. One of the most difficult parts of the procedure is mating the condyle to the fossa because we have to deal with the occlusion as well, and as I mentioned

before, in approximately 20 to 25 percent of the cases I usually move it after that first mating, after I'm able to take the patient's mandible and move it.

Under anesthesia there is some issue as to is that the same muscle tone that the patient will have when they emerge from anesthesia. What we normally do is put the patient in fixation, go back and place the prosthesis, and there is a point where we want to place the prosthesis posteriorally in the fossa so that if there is any pseudo translation, you're starting in a more posterior position, which is why we angulated the head.

We've had the experience where under anesthesia a patient with light in the mating appeared to be adequate. This is the dislocation patient that we dealt with.

When the patient recovered from anesthesia, there was a relaxation of the muscle, and the condyle came forward, and we had to actually replace it. So we recommend actually at the time of surgery to check it with muscle tone and with full paralysis. So at the time we actually check it to make sure that visible when you use the sterile mandibular manipulator, you're looking at the mating of the condyle and the fossa, which you have to do in any system, whether it's custom or stock.

And there's where I think it's up to the surgeon

to make sure that before they leave that operating room, it's optimal mating. But it is surgeon experience that can determine how well that's mated, and it should start in the more posterior aspect of the fossa.

CHAIRMAN HEFFEZ: How do you judge the spacing? Because it's very difficult to judge it completely across the condyle, what the adequate spacing would be between the two surfaces.

Actually it's a good question. Some of the older systems, in the Vitek System there was the recommendation that you put actually a small pad between the condyle and the fossa because it would seat with time, and that was true because it was compressible Proplast in that fossa.

We are recommending that it's just a manual seating without any directional forces from the screws, which is an important question. If the screws are placed in the ramus offset, you can literally drive the prosthesis up against the fossa. So we use drill guides so that we make sure that the screws are placed passively.

The other way you can tell whether there's excessive compression between the condyle and the fossa is literally move it, is to go back to the mandibular manipulator and move it under

direct vision.

CHAIRMAN HEFFEZ: But what is the spacing that you're asking the two surfaces or there is no spacing?

DR. QUINN: There is no spacing. It's direct contact, and then using the drill guide so that the screws don't present any driving forces superiorally.

CHAIRMAN HEFFEZ: Okay.

DR. QUINN: It's a good question. We've had that problem with all of the other systems we've used.

CHAIRMAN HEFFEZ: Because you also have the problem really with the glenoid fossa. You initially had the cement to take out the void, but you really don't know how to judge the void without actually putting the cement in.

DR. QUINN: That's true.

CHAIRMAN HEFFEZ: So any thought given to, for example, using a template to know whether truly the void is significant enough in that particular case?

DR. QUINN: Well, I think the whole issue of void was whether there was significant dead space that would lend to an increased rate of infection from hematoma formation in the dead space under the prosthesis.

CHAIRMAN HEFFEZ: Was it dead space from infection

or stability of the prosthesis?

DR. QUINN: No, because the stability has to be tripod stability that's fit regardless whether there's additional void. If you have tripod stability, and remember the majority of stability comes from the zygomatic arch where the screws are placed, but you're right. There's no way once you fit it to estimate what the amount of void is under the presses.

CHAIRMAN HEFFEZ: Could Mr. Roman address the Part B?

MR. ROMAN: In Part B there was no -- in the fatigue testing there was no set protocol for specifically testing them out of alignment, but just the general nature of potting the components into the test fixtures. There was a little bit of variability there. They weren't exactly set up with each other.

And just a follow-up. It was listed in the testing reports that all of the components were manufactured and were gamma sterilized.

CHAIRMAN HEFFEZ: Do you see any advantage to testing it with offset? Because even though what position you have them in, even if you have them properly mated, the patient doesn't function with them properly mated. The patient really functions with them not mated.

MR. ROMAN: Right. There may be some justification for testing at not exact alignment.

CHAIRMAN HEFFEZ: Thank you.

Janine.

DR. JANOSKY: Janine Janosky.

The question was primarily -- I don't know who would prefer to answer them; probably Dr. Quinn and Dr. Sinn or Ms. Verstynen.

Two issues right now that I'm grappling with. The first is the follow-up, and the second is the use of two primary sites. So since we addressed both of those issues separately, why don't we look at the interaction of those two?

So my primary question is: at what point do you have at least 80 percent of your data available for follow-up? And then from which sites are those coming in terms of proportions?

MS. VERSTYNEN: Mary Verstynen.

Going back to that patient accountability, at every time point we had better than 80 percent follow-up. So that answers the first question.

And obviously the study is pretty much Dr. Quinn and Dr. Sinn. There were only eight patients that were not part of that. I believe that probably one patient wasn't returned to

follow-up from the eight. So the rest of them that were missing follow-up were either at Dr. Sinn's or Dr. Quinn's sites. It's just that the other sites only did one or two.

We had the one site that did five, and they have one patient that is truly lost. We can't locate her. So at all time periods we did have better than 80 percent.

And even to kind of add to my patient accountability slide, I don't know if you noticed, but at the four years we had the best follow-up. There were only, I think, 23 patients out to four years, but the investigators made an extreme effort to try to get all of the patients back in the three-year follow-up.

In some cases it took almost a whole year to get them in. So actually we got a higher follow-up at four years, and actually three of the patients that missed the three-year follow-up were actually seen at the four-year. I think I did that calculation.

If I combined and made a three-year plus and added those four years, the follow-up, I think, was bumped up to 87 or 88 percent, even at three years, which was the lowest follow-up.

So we did have greater than 80 percent then.

DR. JANOSKY: Let me get more specific with my question. If we think that you started with 180 patients in the

study, at what point did you have 80 percent follow-up of those 180 patients? Complete data, 80 percent of them. At what point was that?

MS. VERSTYNEN: The thing is that only at the one month time point were there 180 patients.

DR. JANOSKY: Okay.

MS. VERSTYNEN: Well, no. Actually only at the baseline were there 180 patients because enrollment is occurring as we speak. I'm guessing Dr. Quinn did cases this week. So if you even looked at the one month, there were already ten patients who had missed follow-up because one of the requirements in my data cutoff was that each patient should have at least been for their one month follow-up.

So even at the one month, we had ten of the 180 that missed.

DR. JANOSKY: Okay. So you're down to 95 percent at that point.

MS. VERSTYNEN: Right, exactly.

DR. JANOSKY: So I understand that you have rolling enrollment. That's typically how we do clinical trials in also this type of forward looking study.

But my question is at what point do you have 80

percent complete data of those 180, irrespective of when they were due. So at what point do you have 80 percent of 180 patients?

MS. VERSTYNEN: I calculate the six month point.

MR. CANNER: Maybe we're on the same wave length since I'm a statistician, too, but that's a joke.

DR. JANOSKY: I didn't hear your name earlier.

CHAIRMAN HEFFEZ: Yeah, identify yourself.

MR. CANNER: Sorry. Joe Canner, a statistician with Hogan & Hartson.

I think what you're getting at is take 80 percent of 180, which is -- I can't do the math in my head -- maybe 140 or 150 or whatever, and when those patients would all have three-year follow-up.

I don't know the answer to that, and I think Mary, now that she understands what the question is, can answer that. But I think probably the more relevant answer is that the original sample size calculation for the study was only 86 patients, and FDA has granted Biomet permission to enroll 300 patients altogether, but 86 was the original sample size.

So I think probably a more relevant question would be when 80 percent of the patients will have reached three years among the first 86, and as you can see, we're already up to close

to 50, and so that time frame is probably not very far off, although Mary could probably answer that a little bit better.

DR. JANOSKY: I understood the primary endpoint to be three years.

MR. CANNER: That's right.

DR. JANOSKY: So my question then is at what point do you have 80 percent, which is a liberal follow-up level?

MR. CANNER: Of the 86 that were originally anticipated?

DR. JANOSKY: Of the 180 that were enrolled, and that period of time is at the six month follow-up. If you're going to go with 86, what are you choosing? The first 86 that were enrolled?

Then we get into the issue of what were cemented and what were not cemented, and some of the other issues, but we can leave this point because I'm sure it's going to go throughout the day.

MR. CANNER: Yeah. It's just that --

DR. JANOSKY: But what if we return to the second point. The second point that I had mentioned is that at that point that you have 80 percent follow-up, which is the six month point, what percentage of the patients at six months are Dr. Quinn's and

what are Dr. Sinn's?

It's essentially zero. So we can leave that out. So what percentage are Dr. Quinn's? What percentage are Dr. Sinn's at the six month point?

MR. CANNER: Okay. I'll have to look that up for you now that I understand what you want.

DR. JANOSKY: Okay. I'll return to the issue later so that we can.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

A question for Ms. Verstynen and perhaps Dr. Quinn. One of the issues that FDA charges the panel is to make a determination as to whether the data in the PMAs support the safety and effectiveness of the device for its indicated uses.

You have in your labeling ten indicated uses, but my review of the data says that some of the indications have no data or minimal data, such as use in malignancies or the nonneoplasms. How is the panel to look then at whether there's safety and efficacy and effectiveness are supported for that specific use?

DR. QUINN: That's an excellent question. I think what we have to do is put the numbers in perspective, first, in

terms of the total potential market for a safe and effective prosthesis. I think there are 450,000 hips done a year. Nobody has a very precise way of predicting what is the total population, but I've heard anywhere between 1,500 and 2,500 a year. It defines a very small population to begin with, which I think is appropriate. I don't think this should be widely used unless there were indications.

The more common indications that you saw are osteoarthritis, traumatic arthritis, ankylosis. I think it is reasonable to assume that if a prosthesis is safe and efficacious because the surgical technique would be very similar in a multiply operated joint who has had seven operations, in a joint that has an osteochondroma where there's been no surgery, I would be comfortable making that assumption that it's safe and effective and that indication.

The problem is the numbers. I've probably seen two osteochondromas in 15 years. So I'm not sure whether we'll ever be able to answer that question with the appropriate numbers.

DR. PATTERS: I guess my concern then: should that be included in the labeling as an indication or should the labeling state that there's no data available for treatment of bases with malignancies?

DR. QUINN: I think I'd leave that to somebody more expert in labeling. Does that allow a reasonable surge in the off label indication to use the prosthesis in that rare instance? Because I do think that should be the ultimate outcome for a safe and effective prosthesis.

DR. PATTERS: I'm not an expert in the off label use, but my understanding is that off label use by the practitioner is always available. You know, they accept the liabilities when, of course, there is no specified use in the labeling.

DR. QUINN: Yeah, I'm not sure I'm expert enough to answer it other than what I've said.

MS. VERSTYNEN: Mary Verstynen.

It would be reasonable to add that language to the labeling, and if FDA would agree with that, I mean, it would be reasonable because we don't have malignancies. We probably don't have any benign neoplasms or very few, and maybe we need to qualify that directly in the labeling with either little or no clinical data.

It's a reasonable request.

DR. PATTERS: Thank you.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

I had a question on the radiographic analysis. It said that the heterotopic bone formation was evaluated osseous erosion and fossa resorption. So certainly when you deal with bone and screw into bone, and I think the question was a little bit earlier about screw loosening was never answered.

Was the radiographic analysis standardized or was it done under blinded condition? And how as each of those aspects addressed?

DR. QUINN: Yeah, the radiographic analysis was a Panorex lateral ceph. and a PA ceph. They're standardizing such that sites with the same machines are used. I'm not sure you can standardize them any more than that.

As you know, it's difficult because they are -- at best Panorex is an elliptical tomogram. You are looking for gross osteolysis or gross radiolucencies around them. It is difficult because there's metallic objects. So it would be probably a gross malposition that you would pick up.

The heterotopic bone was probably the easiest finding, but the X-rays were standardized to those three views. Does that answer the question?

DR. COCHRAN: Well, from a standardization, but did Dr. Sinn do the same radiographs at each of the same time points?

That's what I mean by standardization. In the protocol were set radiographs taken at set time points?

DR. QUINN: Yes.

DR. COCHRAN: And then from a screw loosening point of view, the fossa component is the plastic. So that isn't going to get in the way of looking at screws and positioning of screws. I just wondered if there was like a third person or a radiographic investigator who would evaluate the position to see if they had changed.

I think in some of your cases there was some movement in some of the components. I just wondered if there was an independent evaluator to evaluate the X-rays.

DR. QUINN: Well, as I said, we had no device failures. We had no screws, and we had change in the position, but that was gross dislocation. That wasn't movement of the prosthesis itself.

The only finding of note was the heterotopic bone formation. I could let Dr. Sinn address if he followed it the same way, but they were the standard three radiographs based on the baseline films taken postoperatively in the hospital at each landmark.

Now, at the times when we had patients refused, like

for example pregnant patients, we documented that there was a visit without radiographs.

MS. VERSTYNEN: I think to answer that question more directly, with some of our newer IDEs it has become a major issue, and included into our protocols that we have independent radiographic assessments.

This IDE was filed in 1994, and we weren't quite that sophisticated to add that to the protocol. Therefore, each of the investigators did their own radiographic assessments.

DR. BURTON: Richard Burton.

A question for Dr. Quinn. On your technique portion which you published, and Step 4 talks about performing an osteogomy, and they have a traditional condylectomy, and then once you're able to retract the stump down, it talks about removal of a larger segment of the cordite, and it wasn't clear in reading some of the other surgical materials whether or not a coronoidectomy was included with that.

Then in your adverse events there were 15 joints that required an additional coronoidectomy to improve I would assume range of motion associated with that.

Is that a long enough time frame out that there was regrowth, reformation of the coronoid? And is that actually a

standard portion of the procedure is a coronoidectomy?

DR. QUINN: It's not a standard. I think in the multiply operated joints where they start with large restriction of motions, I'd recommend that the way to do the two-step osteotomy is the second osteotomy is to include the coronoid in it in a one piece step, and we've designed instruments to do that.

I do think that the 15 cases show that early on there are probably cases where we should have removed it because you have the option of making almost a C cut. The way you determine how much bone you take off is once the fossa implant is in place and you put the patient in fixation, if you haven't removed enough bone, you will actually hit the lip of the implant with the superior edge of the ramus. That determines how much bone is removed.

I think it's surgeon dependent whether they determine whether to take the coronoids off at the time. I think in multiply operated patients who start with a ten millimeter size, I would remove it.

If they were largely being operated on more for pain than mechanical obstruction, it's not necessary that all of the coronoids have to be removed.

DR. BURTON: Okay. Thank you.

CHAIRMAN HEFFEZ: Dr. Li.

DR. LI: Steve Li.

I have a question for the designers of the device, perhaps Mr. Roman.

The one thing that I'm a little uncomfortable with in your prosthesis design and the fossa design is -- let me make sure I understand it. The fossa component is fixed with what, five screws through the polyethylene to the bone?

MR. ROMAN: That's correct.

DR. LI: So typically we don't -- I would say generally designers typically don't fix polyethylene directly with screws. When the polyethylene would be under load because of the creep that's going to occur, and so on the fossa I would never expect the bone screws to pull out because if there's any load on the polyethylene, the polyethylene is going to creep and essentially make the screw holes bigger and the fossa component would become loose.

So in general, you never see or hardly ever -- this is the only device I've ever seen where the polyethylene is actually screwed to the bone to accomplish the load.

So my question is: have you ever looked at the change in the fixation of the polyethylene to the bone before and after loading?

And perhaps, Dr. Quinn, if you've ever noticed on retrievals if the polyethylene component is actually looser than it was, because we see this on total hips and total knees. Even after a six month period if you do a measurement of the fixation of the polyethylene to a metal backing, that fixation loosens relatively rapidly even when the whole component is fixed, and now you've got five individual screws that are much higher stress concentrators.

So I would predict that eventually that polyethylene would become loose from the screws, and that's a long way to ask: have you ever looked at that? And is there a way to measure that off of your fatigue tests?

DR. QUINN: No. That has not been looked at specifically, but the design of the fossa screws does have a flat portion on the under side of the head that serves as basically a washer. So we are basically sandwiching the polyethylene between the under side of the head and zygomatic arch.

As far as if that's been looked at from explants, I don't know.

DR. QUINN: No. The four that were removed were for infection, and we didn't find any loose screws or mobility in the fossa implant itself. Just correction. It's a minimum

of four screws. They had 2.0 millimeter, and they were designed, especially designed 2.0 millimeter with a broader head to give that washer effect.

DR. LI: But that won't affect creep in the superior/inferior direction, will it, unless I've got my orientation wrong?

In other words, you know, it's a three dimensional piece and that washer effect protects you in one direction but not the others, and if the polyethylene is loaded against the screw, it's going to creep.

And so the chance, I think, of it remaining tight forever is near zero. So it may be tight enough to be clinically successful, but I can't imagine that it's after a million or 500,000 loading cycles that it, in fact, is fixed with the same tightness it was at the moment you fixed it.

DR. QUINN: I'll let Shawn answer it. I didn't see any clinical, but I obviously am not examining for creep in the screw holes when we have removed them. I don't know whether the test was specifically done because it was done at an offset to see if we would fracture it at the junction between the horizontal and perpendicular aspect of it, and I latched on to see if there was any other test done other than seeing whether it fractured.

DR. LI: Well, for instance, on that test you mentioned, had you measured the amount of micro motion before and after that test, you might have gotten some indication for if it's going to loosen, but that you have to measure because remember 100 microns is more than enough to cause sufficient motion to change the biomechanics and the wear properties.

So this might not be something you could casually feel. You would actually have to go in and measure it and actually see, but the effects could be cumulative, very large.

DR. QUINN: Measure it in vivo or?

DR. LI: In vivo is tough, but even in the laboratory test you could make some attempt to measure that, but certainly clinically as these patients get out longer, when you get out to five, six, seven years, I think that would be something I recommend you look at very carefully, is the fixation of the plastic component.

The screws are going to be intact. It's the plastic, I think, that's going to move independently of the screws.

CHAIRMAN HEFFEZ: I'd like to move on with Ms. Helms and followed by Ms. Howe.

MS. HELMS: Thank you.

Elizabeth Helms, and I'm going to follow up with

the loading issue because I think it's so vitally important, especially since I'm a patient that had two open joint surgical procedures, condylectomy and no implantation and have done really well.

But you know, malocclusion of a Class II or Class III, where there is a deviation or an asymmetrical mandible, was the testing done other than just rotating? Was there testing done where the job deviates, where that would increase the load on that joint and allow the joint to move at that deviation point?

That's my first question and you can respond to that.

MR. ROMAN: I did want to clarify from the earlier discussion of the fatigue testing. As I discussed, in the testing the mandibular components were angled at a ten degree angle to place them in a worst case scenario, both subjected the ramal plate to a large bending moment, and also minimized the surface contact between the spherical head of the mandibular component and the spherical seat of the fossa component.

MS. HELMS: Okay. Then were there any studies done in the follow-ups where there was a unilateral joint? Was there any degeneration or increased stabilization to the opposite joint?

MR. ROMAN: Let me go back because I think Dr. Heffez raised the same issue. I think it's a very important issue. When

we placed the condyle in the fossa, I don't know of any methodology to know exactly what happens to that seating. The relationship to the condyle and the fossa, which I think is what Dr. Heffez was getting at, when this patient now wakes up, has muscle tone and functions.

I doubt it's in the exact place we place it surgically. That would be counterintuitive. The reason we designed the condylar head as such a large, spherical head is to allow for some of that because I think it's impossible for us to know at the time of surgery that this is exactly where this patient will function.

Your second question is a very interesting one, and that is when you place a prosthesis unilaterally and you have a normal functioning joint that has a lateral pterygoid, you've got two different tires on a car.

I mean, I've heard surgeons who are much more aggressive than I am say if you put one in, you should put both in. I think that's overly aggressive.

Theoretically they would function better because you would have two systems that have no rotation and -- I'm sorry -- translation and just rotate. I think there's a point at which when you send patients for physical therapy after joints especially

unilateral, I'm less concerned with achieving 30 millimeters. I'm worried about people going further. These aren't designed to do that.

And I think it's more problematic when you have one prosthetic joint and one natural joint because at about two thirds of the opening, you start to get the lateral pterygoid muscle on the contralateral side take over. The prosthetic joint stops moving, and you see deviation.

So our bigger problem is we've been surprised how good the results are in increasing the intercisal opening. I'm worried by people who say, "I think I can go to 40 millimeters," because I don't think these joints are designed to do that, and it's more of a problem in the case you describe where there's a prosthesis and an otogenous joint.

Does that answer your question or is that --

MS. HELMS: Half way.

CHAIRMAN HEFFEZ: Ms. Howe.

MS. HOWE: Elizabeth Howe.

My question is kind of a blend of both the need to do professional training as well as this lost follow-up, the question being: was there any thought given to using sites three and four to do follow-up data collection enabling people who might

be on the other side of the country to actually have that data collection done?

DR. QUINN: No. It's a good suggestion. We did not do that.

CHAIRMAN HEFFEZ: Dr. Hewlett.

DR. HEWLETT: Edmond Hewlett for Dr. Quinn again.

Your presentation as well as the proposed labeling indicate that occlusal relationship changes may, in fact, occur as a result of the placement of the prosthesis. In your protocol was there any provision made for assessing occlusion postoperatively and then treating any potential interference, say, with a splint in order to eliminate occlusion as a possible etiology in the adverse events?

DR. QUINN: Part of the follow-up form is the occlusion checklist. What's the intercisal opening? Is there an open bite? Is there a cross bite? That's part of all the landmarks.

The question is: was the preexisting occlusion secondary to the temporomandibular joint or vice versa? And that's a chicken and egg question I don't think anybody can answer.

The point we made with the prosthesis is you have the ability to change the occlusion. So if you started with what

we've seen, some of the idiopathic female condylar resorption, where we see females, late 20s, early 30s, who have marked resorption of condyles that become Class II, there you know that the malocclusion was secondary to the temporomandibular joint disease, and there's a case where I think if we were going to place the prosthesis, we would try to improve the occlusion.

I don't think we would just try to improve everyone's occlusion who had a prosthesis, but when the malocclusion is secondary to the temporomandibular joint disease, it is something that you can address with the prosthesis.

CHAIRMAN HEFFEZ: Is your question answered, Dr. Hewlett?

DR. HEWLETT: Well, I guess. Yeah, maybe just to clarify, I think I'm referring specifically to any assessment in addition to the assessment they outlined. Any functional assessment?

DR. QUINN: Oh, I'm sorry. Yeah, it is common, and it wasn't something we reported because I do think it's part of normal post surgical that we do occlusive adjustments. If somebody came in two months later and had a very high contact on a canine, we will adjust it.

Most of these patients, we try to get them off

splints.

DR. HEWLETT: I see.

DR. QUINN: If at all possible.

CHAIRMAN HEFFEZ: A couple of quick things, and then I'd like to move on to the FDA presentation.

One is at one point in time you were removing the peg. How were you doing that?

DR. QUINN: Dr. Sinn and I both agreed that we would use a rongeur and simply clip it at the surface of the inner surface of the fossa.

CHAIRMAN HEFFEZ: And how many cases were done with them clipped?

I understood -- and I may have not gotten the date right -- was it February 3rd, 2000 that you stated to use the manufactured glenoid fossa without the peg?

DR. QUINN: Actually the fossa was manufactured without the peg, and I believe Dr. Sinn used three of them that were manufactured without the peg, and then the FDA was notified. So the majority of them were clipped, were actually separated with a rongeur. Only three were pre-manufactured without the post.

CHAIRMAN HEFFEZ: So in this whole study we only have three cases where the peg -- manufactured without the peg;

is that correct?

DR. QUINN: That's correct.

Do we have the numbers up?

CHAIRMAN HEFFEZ: Fine.

DR. QUINN: Okay.

CHAIRMAN HEFFEZ: Okay. Dr. Runner.

DR. RUNNER: This is Susan Runner.

I just want to ask the company if you could clarify. We've gone around and around about the numbers here, and we keep bringing up the number 180 patients. It's not 180 patients. It's 168 patients and 180 cases.

Could you clarify that? Because I think we keep rounding these numbers around, and I want to be sure we're talking about the right numbers.

MS. VERSTYNEN: Mary Verstynen.

Since we had both unilateral and bilateral patients enrolled into this study, we found out early on that there were actually patients who were enrolled for one side and later on the other side was enrolled, meaning they would have different surgery dates for the two sides.

So the cases are defined by the surgery date so that we could follow the patients because literally we have patients

that had maybe the left put in at one point and one year later have the right.

And in order to manage the clinical data and to keep the follow-ups on track, then that other side later on became a second case. As it turns out, there were 12 patients that had -- it turned out in the end to be bilateral cases, but they had different surgery dates for the side. So as it turns out, there were 168 patients in the study defined as 180 patients or 80 cases.

Does that make sense?

There were 12 patients that had different surgery dates for the two sides. If one bilateral patient who had surgeries of the sides on the same surgery data it was considered a case. So it all came back to the definition -- the surgery date.

CHAIRMAN HEFFEZ: Okay. Just for the panel, I would like to also for clarification understand if you can repeat to us the cement versus the noncemented cases, when the cement cases were no longer performed, numbers, so that it's a little clear because we are throwing around different numbers of two populations.

MS. VERSTYNEN: Right. There were 38 cemented cases, and I believe in the clinical report it was in August of 1998, was when the last cemented case was done.

Therefore, all of the cemented cases are actually incorporated into the cohort, which are three years or longer out.

CHAIRMAN HEFFEZ: So how many cases, noncement, have been followed through for three years plus?

MS. VERSTYNEN: Eleven.

CHAIRMAN HEFFEZ: So the 11 cases, noncement, followed for three years plus?

MS. VERSTYNEN: That was in the cohort, yes.

CHAIRMAN HEFFEZ: Okay. Then the other thing I want to do for the panel is I want to make sure, Dr. Janosky, you feel comfortable with all of your questions answered.

DR. JANOSKY: I was going to return again to it after FDA's presentation or this afternoon.

CHAIRMAN HEFFEZ: Okay. So if we've exhausted the questions, at this point in time I'd like to suggest perhaps a 15 minute break. So that you understand, it's 10:15. Precisely at 10:30 we will start.

(Laughter.)

(Whereupon, the foregoing matter went off the record at 10:15 a.m. and went back on the record at 10:30 a.m.)

CHAIRMAN HEFFEZ: I'll ask everybody to take a seat.

Okay. I would like to get started. Before I do get started with the FDA presentation, I want to announce a change in the schedule. Following the FDA presentation, we'll go right to open committee discussion, which our primary reviewers will present, and discussion.

We will break for lunch from 12:30 to 2:00 p.m. So that's a change. Lunch will be from 12:30 to 2:00 p.m. We will start precisely at two o'clock. So I ask everybody to be back in the room at two o'clock and then the rest of the schedule will follow.

So without further ado, Dr. Susan Runner.

DR. RUNNER: Good morning. I want to thank you all for coming and deliberating on this important issue this morning, and I would like to start out by introducing the FDA primary review team.

We have Ms. Angela Blackwell, who's the lead reviewer and the engineering reviewer.

We have Dr. Kevin Mulry, who's the clinical reviewer.

And we have Ms. Phyllis Silverman, who's the statistical reviewer.

Before we hear the FDA review team, I'd like to sort of step back and set the stage by reminding you of the importance

of the history of the patients in whom this device has been implanted.

As you all know, the term "temporomandibular joint disorder" is a complicated term and a collective term. It has a lot of different definitions by a lot of different people, and the treatment strategies range from reversible therapeutic approaches to highly invasive procedures.

There is, however, a patient population for whom nonsurgical treatment is not an option, and these patients have often undergone numerous surgical procedures which leave them debilitated, in chronic pain and with limited options.

Presentation of the FDA review will begin with Ms. Angela Blackwell's presentation of the engineering review. Then Dr. Mulry will present the clinical review and the statistical review. Ms. Silverman will be available for questions on the statistical section.

At the conclusion of our presentation you will be able to ask FDA any questions.

MS. BLACKWELL: During the course of my engineering review I will discuss the materials, the component testing, system fatigue testing, and the outstanding engineering issues.

The materials of the fossa component is ArCom ultra

high molecular weight polyethylene. The materials of the mandibular component are cobalt-chromium--molybdenum alloy and titanium alloy plasma spray. All of these materials are commonly used in orthopedics, and they all meet standards that are recognized by FDA.

Component testing. There were several types of component testing, including static testing, pull-out testing, and push-through testing. These were all done to demonstrate that the device was adequately -- had an adequate strength for insertion and use.

Static testing of the mandibular components. At 576 pounds, the net portion bent with no breakage. This is well above the 20 to 200 pounds reported for bite force in the dental literature.

Static test of the fossa flange. It bent at 83 pounds without fracture. This was a test just to make sure that the flange would take some force. There's not an in vivo situation where this would occur.

Fossa screw push-through. Eighty pounds was required to push the screws through the fossa. Three hundred and seventy-three pounds was required to pull the screws out of bovine cortical bone.

The component testing indicated that the device strength exceeded the insertion forces, but fatigue testing is needed to more completely evaluate device strength during use.

Fatigue testing demonstrated that all of the components working together will last for the expected lifetime of the device.

Device failure is very common in this patient population. Fatigue testing is used to estimate useful life span of the device.

Fatigue testing of the fossa and mandibular components. Cyclic compressive loading for the maximum load of 145 pounds for ten million cycles results with no failures in the five samples. Literature estimates a non-bruxing patient would load the joint with a force of between 20 and 100 pounds.

This testing was adequate to show the devices will survive five to ten years under a load of 145 pounds.

We still have one concern remaining. This deals with the post removal. I think the company mentioned it earlier in their presentation. The original design had a post, and after I think 30-something patients the surgeons started removing the post.

And then in February 2002, when the company realized

that all of the posts were being removed, they came in with a new design that didn't have the post. So we asked them for additional fatigue testing to address these concerns.

They're using the same type of testing that they used before. So hopefully we'll be able to compare the previous results with the fossa design without a post and the fossa design with a post, but with the post removed by rongeur.

This test is currently being conducted. I believe they have four samples of each of these done at this time, and they've run out with no failures. So we expect the final report early next month.

DR. MULRY: I'm going to present the FDA scientific review of the clinical data submitted in the PMA.

CHAIRMAN HEFFEZ: This is Dr. Kevin --

DR. MULRY: Oh, I'm sorry. I'm Dr. Kevin Mulry, and this is the clinical review.

Thank you.

FDA is requesting the panel's input today on this pre-market approval application, and the topics I'm going to discuss are the previous TMJ treatment, the device descriptions, indication for use, the clinical study results, the investigational sites and the investigators, adverse events, fossa and bone cement,

and questions for the panel.

In advance, many of these topics have already been discussed previously by the other sponsor's presentations. So what I'll do is I'm going to run through just the points that I think will emphasize the issues that relate to the questions for the panel that we would like you to address today.

The clinical review of the PMA involves a careful consideration of all of the data presented in the application. You, the panel, recommend based upon the data presented whether you believe the device is safe and effective for its intended uses.

Since there are risks associated with any device, your recommendation must consider whether the demonstrated benefits outweigh any known or possible risks.

Next slide.

Before I begin presenting the clinical data, I think it's important just to reemphasize again the previous treatments that these patients that are enrolled in the clinical trial have had, and we look and we see approximately 70 percent of them have had nonsurgical treatment. Over 60 percent have had disrepair. Almost 40 percent have had silastic disc. We've had Proplast grafts, total joint prostheses, partial joint prostheses.

So they've had quite a bit of treatment in advance

of enrolling in the study. So success for these patients may be limited based upon the sequelae of the multiple surgeries of the previous treatments.

And we've already kind of gone over this, and I don't think there's any need to emphasize this too much, but the one point we want to focus on here today is the fossa with the post and just the fact that that post is the original design, and that it has been used in the vast majority of cases either as the post, the design picture here, or with the post removed with the rongeur.

The other thing I'd like to emphasize of it is that this is a stop device, and it's only intended for total joint reconstruction and not partial reconstruction.

You can move on. Next slide.

And also we have had an adequate description of the mandibular condyles, the standard size on the left and the narrow on the right. There is, as they described, a third design, the offset design, but that has not been used in the clinical study to date, and I do have samples of these devices which I will pass around after the presentation.

The indications for use I think have been adequately vetted. The important thing we want to emphasize here is that FDA is seeking your input on the applicant's proposed indications

for use and the data presented to support these indications, and I think you've already started that discussion.

We can move on.

I think we've had adequate discussion of the primary efficacy endpoints that's on the ten centimeter scale, and we're looking for the changes on that VAS scale.

Success criteria. I'd just like to go over this real quickly, although this has already been discussed, that the success has two phases to it. One, a patient is determined to be a success if the patient has not had a permanent joint removal.

The second aspect is the patient has to meet two of the following criteria, either a reduction in pain of one centimeter on the VAS scale; a reduction in interference with eating by one centimeter on the VAS scale; or an increase in maximal incisal opening of ten percent, and that's all from baseline to the three-year follow-up point.

And the clinical study's success was defined in the protocol as 60 percent or more of the patients who at implantation of the device, having met the above patient success criteria at three years' follow-up, 60 percent.

We do have, as we just discussed, as Dr. Runner did question the sponsor regarding the issue of cases and the

numbers of patients, I just want to reemphasize there were 180 total cases in this study, but there were only 168 total patients.

The clinical study had the 180 cases. To date we have 143 cases at the six month follow-up, 89 at the one and a half years' follow-up, and then we have 45 at the three-year follow-up, and the sponsor is terming the three-year follow-up or the 45 cases as the unimputed cohort, and these are the sponsor's terms, not FDA.

FDA views the 45 cases, which represent 25 percent of the total cases, as the final three-year data.

In looking at the clinical study results, we have the primary efficacy endpoints of jaw pain intensity, interference with eating, and maximal incisal opening. I'd like to shift to the right-hand side of the slide where we have the cohort of 45 that were evaluated at the three-year follow-up visit, and what we're looking at here is the difference between visit one pre-operative, and visit eight three-year follow-up visit.

The difference in the change in the jaw pain intensity was approximately 5.7 centimeters on the VAS scale. The interference with eating was approximately 5.8 centimeters, and the maximal incisal opening, we see an increase of about 10.27 millimeters.

We're not going to discuss the imputed cohort at this time because we feel that the 45 patients that were actually evaluated at the three-year follow-up are the data that we think is the more relevant data.

The T test analysis that was done on this data shows that in the total group there was a statistical difference in all three primary endpoints between baseline and assessments at all time points from one month follow-up to three years' follow-up.

And for jaw pain intensity and interference with eating, over 80 percent of the improvement was experienced by six months with the maximum incisal opening approximately 97 percent of their overall effect of improvement occurred by six months.

So generally, the results plateaued around six months, and from there on we didn't see much change in the results or the outcomes. So the question for the panel is whether the results for jaw pain intensity, interference with eating, and maximal incisal opening for the cases with three-year data which represent 25 percent of the implanted population adequately represent the expected outcomes for the total study group of three years.

One clinical study, as Dr. Quinn has presented already, was conducted to support this pre-market approval

application, and the thing I want to emphasize here again is that we look at the fact that 132 of the 180 cases were treated at site one and 40 at site two, and the remaining eight were at the other three remaining site.

A multivariate analysis noted a significant interaction between time and investigational site with jaw pain intensity at site one. The cases began with a much higher VAS score of about nine centimeters versus approximately 5.63 at the other sites combined and also experienced a relatively larger amount or improvement over time compared to the other sites.

So the question for the panel is whether the fact that 96 percent or 172 of the 180 cases were treated at only two sites. Does this present a potential for bias in the clinical outcomes?

Next slide.

As far as adverse events go, actually it should be 51 of the 168 or approximately 30 percent of the patients have reports of adverse events, and I think Dr. Quinn has adequately described that most of these adverse events related to excision of tissue, either the neuroma or heterotopic bone, facial trauma, motor vehicle accidents, coronoidectomy or ear problems, ear infections.

Eight patients required permanent device removal, and two of those were fossa components due to necrosis, infection, and swelling; five total joints due to pain, swelling, infection, and ankylosis; and one mandibular component due to dislocation.

I think it's most important to note, however, that 117 of the 168 or approximately 70 percent had no adverse events at all.

Now, the 30 percent adverse event rate may appear to be high. However, I think it's important to emphasize that most of these adverse events resolved themselves, did not required device removal, and met the success criteria.

The issue for the panel is to discuss the rate of adverse events in this patient population.

I just wanted to emphasize here that the purpose of the post on the fossa was to facilitate retention of bone cement, and as I think we just discussed prior to the break, the use of bone cement was discontinued in August of 1998, and of the 180 cases, 38 or 21 percent had bone cement used and 142 or 79 percent did not.

And the issue for the panel here is that the company plans to market the device as a noncemented fossa or as a cemented fossa. In the clinical data set, some of the cases are with cement

and some cases are without cement, and the panel needs to discuss the data in light of these two different methods.

In summary, the results of the analysis of the primary efficacy endpoints demonstrate that approximately 98 percent or 44 out of the 45 cases were successes well beyond the 60 percent which was the definition of success in the protocol. The success criteria for jaw pain intensity and interference with eating was one centimeter. However, the improvement of approximately five centimeters was well beyond the success criteria, and for the maximal incisal opening the improvement was beyond the ten percent needed for success.

Patient satisfaction was over 90 percent of all visits up to three years. As previously noted the patients enrolled in this clinical trial were selected only after nonsurgical treatment had failed or after a previous implant failure and also after a history of an average of 5.2 previous surgeries of the TMJ area.

Success of the surgical results from this reconstruction must often be tempered by the realization that reduction in painful symptoms and increase in function may be limited at best. To date the clinical study results had exceeded the criteria for success.

As I noted at the beginning of this presentation, we are seeking your input today on the applicant's proposed indications for use and the data presented to support these indications, and what I'd like to do is just run through the questions that we would like the panel to address today.

Question one, can the results for jaw pain intensity, interference with eating, and maximal incisal opening for the cases presented with three-year data which represent 25 percent of the implanted population adequately represent the expected outcomes for the total study group at three years?

Question two, 132 of the 180 cases were treated at site one, Dr. Quinn. Forty of the 180 cases were treated at site two, Dr. Sinn. Eight of the 180 cases were treated at sites three, four, and five combined. Does the fact that 96 percent or 172 of the 180 cases -- the fact that they were treated at only two sites present a potential for bias in the clinical outcomes?

Question three, 51 of the 168 implanted patients have reports of adverse events. Of these 51 patients, eight required permanent device removal. Please discuss the rate of adverse events in this patient population.

Number four, the company plans to market the device as a noncemented fossa or as a cemented fossa. In the clinical

data set, some of the cases are with cement and some cases are without cement. Please discuss the data in light of these two different methods.

Question five, the sponsor has provided engineering test data and a protocol for testing on both the new fossa design without a post and the fossa with a post removed using the rongeur. Do the engineering test data and protocol as presented give adequate safety and effectiveness information on this device?

And the last question, (a) FDA has reviewed proposed labeling. Please discuss the draft labeling as presented.

(b) Please discuss the need for training and the type of training protocol that may be necessary for safe and effective use of this device.

(c) The sponsor intends to complete the pivotal PMA study following all patients for three years. Please discuss the need for any additional post market studies and issues that should be addressed were those studies to be required.

Thank you for the opportunity to present, and Ms. Blackwell and I will be happy to answer any questions you might have.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

I have a question actually for Ms. Silverman if that would be all right.

CHAIRMAN HEFFEZ: Sure.

DR. PATTERS: Does FDA have an opinion on the definition of a case and how that definition was applied to these studies as a case being a surgical procedure, whether it be replacement of one joint or both joints, and that replacement of both joints at two different times would be two cases? Do you have an opinion on that?

MS. SILVERMAN: That is not a statistical question.

Phyllis Silverman.

That is a clinical question. That really isn't a statistical question.

DR. PATTERS: Well, how does one handle the statistics when some individuals have a single surgical procedure as defined as a case and some individuals have two surgical procedures defined as a case such that there is twice the likelihood of failure in someone who's had two procedures even if done at the same time than someone who has done one procedure?

MS. SILVERMAN: Right. In this data set the people that were considered two cases, the 12 patients that were considered two individual cases, I believe they were treated as if they were

independent cases, and because it was such a small percent of the total population, I didn't make an issue out of it.

Generally if you would have bilateral cases, then you would have to account for within patient correlation. You'd have to do slightly different statistics, but in this data analysis I let them treat it as individual cases.

DR. PATTERS: Thank you.

DR. JANOSKY: Ms. Silverman, I was hoping to catch you before you walked away. So would you mind? I want to follow in that vein, but I want to take a little bit further.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky. Sorry.

If I take a look at the plots that the sponsors have provided and I look at the three baseline data points and they're graphed, I can tell by looking at those graphs at baseline that those are not symmetrical distributions.

Given that point of information, the second point of information is there's a controversy in statistics as to whether Likert type VAS scales should be analyzed as parametric or nonparametric techniques.

Taking those two points together and also adding the third point that was just discussed about data being dependent

and treating as independent, were there other types of analyses that were done that would have taken into account all three of these issues?

MS. SILVERMAN: Well, they could have done a nonparametric analysis to show how it compared to the parametric, but I did not request that. They did a repeated measures analysis, and I thought that that would account for like some within patient variability and stuff, but I did not request any other analyses.

DR. JANOSKY: That was your decision? That was the sponsor's decision? How was that decision made?

MS. SILVERMAN: Well, the sponsor chooses what kind of analyses they wanted to do, and we can request additional analysis if we thought that they were necessary, but when I looked at the overall picture I thought it was pretty dramatic, that the effect was pretty dramatic, and I did not ask them to do a different kind of analyses.

DR. JANOSKY: So given the analyses that were done, did the sponsor provide any information to show that the statistical assumptions were meant for those particular techniques?

MS. SILVERMAN: I don't believe they did.

DR. JANOSKY: Thank you.

CHAIRMAN HEFFEZ: Any other questions? Dr. Li.

DR. LI: Steve Li.

A question for I think it's probably Angela on the mechanical testing.

There was a fatigue test where the fossa and mandibular component was placed in fatigue.

MS. BLACKWELL: Yes, there were several.

DR. LI: Right, and the conclusion, I think, on those was that there was no failure of the components.

MS. BLACKWELL: Yes.

DR LI: So my question is: what was the failure criteria for the fossa component?

MS. BLACKWELL: What was the failure criteria?

DR. LI: In other words, how would you know? What would have counted as a failure for the fossa? Did it have to break?

MS. BLACKWELL: Breakage, fracture.

DR. LI: So if there was severe wear or deformation, would that have counted as a failure criteria?

MS. BLACKWELL: I believe so.

DR. LI: So at these loads, there was no deformation and no wear in the fatigue tests?

MS. BLACKWELL: They didn't do microscopic level

analysis. So you couldn't get a definite answer on that from the test protocol.

DR. RUNNER: I think maybe the specifics of the test protocol might be better answered by the sponsor in terms of --

DR. LI: Okay. That would be a whole -- I'm sorry. I didn't mean to --

MS. BLACKWELL: Yes. Well, also bear in mind that the gentleman who's here today, he didn't do the tests that we're talking about. It was done like eight years ago or something.

DR. LI: Well, my general question is you're doing a test and then saying the components pass, but I don't know what the pass-failure criteria is other than frank breakage.

DR. RUNNER: Angela, I think you should have the company answer that question.

MS. BLACKWELL: Yeah.

MR. ROMAN: Shawn Roman.

The acceptance criteria, there are two things looked at for the fossa compliance. As Angela mentioned, they are looking for a fracture or breakage of the fossa component, and also on a macroscopic level looked at where on the fossa component, you know, and on the articular surface.

DR. LI: That was just a visual surface is there

wear or is there not wear.

MR. ROMAN: That's correct.

DR. LI: How about deformation?

MR. ROMAN: Yeah. During the visual inspection of the fossa component?

DR. LI: So there was no indentation of the metal into the plastic after this test?

MR. ROMAN: No, sir.

DR. LI: Do you find that a little unusual, given that you have a high load, small area, millions of cycles, that there is no indentation?

MR. ROMAN: Given the large surface contact between the mandibular component and the fossa component, I would say no.

DR. LI: Because even in a total HEP, we just got a much larger surface area. There's definite deformation under these similar conditions. So if there is no wear and no deformation, one I think is the follow-up question to somebody else. The load may be going somewhere else, right? Because certainly there's enough load in there that should cause wear or deformation on the polyethylene was exactly mechanically appropriate.

So one question would be a closer examination of the materials of construction and how the implants are fixed and

just exactly where is the load going.

MR. ROMAN: The point was brought up that that is something that we can take a look at now because we are currently running fatigue testing to address the issues between removed fossa posts and posts that are -- or I'm sorry -- fossa components that were manufactured without the posts.

DR. LI: Okay. Obviously my concern is you're undergoing another set of tests to test a component without the post, but I can't see how it would help but pass under the current conditions of the test.

MR. ROMAN: Okay.

DR. LI: So under those conditions, I'm not even sure why you would particularly run that test if there's really no way for the polyethylene to fail, if you see what I mean.

DR. ANSETH: Kristi Anseth.

And just one quick follow-up. So in the studies that you're undergoing right now with the non-post fossa, there will be no other further analysis, the wear or anything other than macroscopic.

MR. ROMAN: That's something that we can. We can include a more microscopic analysis of the fossa bone that's deemed necessary.

CHAIRMAN HEFFEZ: Dr. Li?

R. LI: I'm sorry. I'm back to one one last -- I'm on the fixation issue. I think the test you did was, if I remember right, was a screw pull-through. You tried to basically measure the amount of force it took to pull the screw through the hole, which obviously was described as not really an in vivo number, would not have been a much more useful number to essentially apply a small load. So you cycle the plastic in and out of the screw and see how long it takes actually to pull the screw that way, that way through because that's the way it's going to fail. It's not going to rip out in one giant pull, but it probably will loosen if you apply kind of an in and out motion along the axis of the screw.

MR. ROMAN: It's my understanding though the fossa component does not see a cyclical load in the sheer direction. So --

DR. LI: Well, I'm sorry. Pick it in the other direction. I mean it doesn't really matter in what direction. I think it's going to move.

MR. ROMAN: In the other direction, you would have this over the temporal bone, keeping that micro motion from occurring.

DR. LI: So it's fully supported on the superior?

MR. ROMAN: Yes.

DR. LI: Okay. I didn't catch that on the drawing.

CHAIRMAN HEFFEZ: Ms. Helms.

MS. HELMS: Thank you.

Liz Helms.

My follow-up. On the 12 patients that went from unilateral surgery to bilateral surgery, of those 12 patients was there cause from the load going somewhere else, or was that a condition that was present and needed to have treatment and you decided to wait on that? What were the circumstances of those 12? Either, either?

DR. QUINN: Yeah. Patients who had initially one --

CHAIRMAN HEFFEZ: Dr. Quinn.

DR. QUINN: I'm sorry. Dr. Quinn.

You asked the patients who initially had one side place and then had a sepsis contralateral side?

MS. HELMS: Right.

DR. QUINN: Okay, and what was the question about?

MS. HELMS: Okay. The question was what was the cause of those other 12 to come back and have the other side done.

DR. QUINN: I'm not sure what was the cause. Usually the two reasons patients get prosthetic plates are usually mechanical difficulties. It's relatively easy to make the decision when they are fused, but when it's pain, since it's so subjective, normally patients are largely the decision maker as to what side might be.

We ask them in terms of their pain if the pain level is a nine out of ten, but it's 90 percent left sided and they're functioning on the contralateral side, we will replace the one joint.

I think the issue that Dr. Janosky raised about how do they play into the statistics, and I'm not a statistician, but it's difficult for us to follow them when they're bilateral joints unless we separate them clearly because they'll come in and say they have pain, and we have to side that pain. So that is one of the reasons we did separate it out.

The major reason for coming back hopefully in this study was that was that they were pleased enough with the results in the reduction of pain and the increase in function on the first set that they requested the second.

The only other reason it would be is -- and I can't speak to this with all of these patients in mind -- at the time

of surgery because this is not a knee; it is one bone with both joints in there. It is sometimes difficult for us to determine which side is actually causing the ankylosis. We could have radiographic evidence of fibrous or bony ankylosis, but it's sometimes difficult.

There are times that we get permission to replace both joints. We will go into the worst joint radiographically and pain-wise and sometimes stop because if we do achieve 30 to 33 millimeters with replacing one joint, it will stop. Because if we do achieve 30 to 33 millimeters with replacing one joint, we will stop.

It is the pain issue that I think largely drives the second side being done and patients will say, "Now this one is bothering me, and I want the same result that we got from the first side."

CHAIRMAN HEFFEZ: I think her specific question was she wants to know whether the surgery on one side caused deterioration on the contralateral side; is that correct?

MS. HELMS: Right. Do you know if any of those 12 was there a shift in the load to the opposite side where the patient originally had not presented with a problem to the opposite side. So there was just a decision to go ahead and do a unilateral implant

rather than a bilateral implant.

Was a load shifted to the other side after the implant was done that created degeneration in that other joint?

DR. QUINN: That's a good question. I don't know of any way of measuring that. The attempts to measure intra-articular loads have been less than optimal. I'm not sure how you can measure that.

But if patients have a progressive degenerative disease as osteoarthritis, it is potential that they could continue that degeneration of the non-implanted side, and I think that's the most common we implant the second side.

CHAIRMAN HEFFEZ: Thank you.

Dr. Janosky.

DR. JANOSKY: The question is for Dr. Mulry and Ms. Silverman.

I want to return to the question that I raised to the sponsor this morning, if we could address it together a little. On your slide you have clinical study cases, and let's just use case to be whatever they're defining case to be irrespective of whether that side or not, just to deal with the issue for a second more simplistically.

Their primary endpoint was three years.

DR. MULRY: Yes.

DR. JANOSKY: For the study, and based on what you had presented in the slide and based on what I have gathered from the information, they had presented is that out of 180 cases at year three, you had 45 cases.

DR. MULRY: That's correct.

DR. JANOSKY: To which you had complete data.

DR. MULRY: That's correct.

DR. JANOSKY: Which given the issue that I was talking about this morning in calculating follow-up, you calculated that there would be a 25 percent follow-up.

DR. MULRY: That's correct.

DR. JANOSKY: Now, one of the questions I asked the sponsor this morning was: out of those 45 cases, what number came from Dr. Sinn and what number came from Dr. Quinn. Do you have that piece of information for us?

DR. MULRY: No, I don't believe we do.

MS. SILVERMAN: I do know that all 45 were at those two sites, but I don't recall what -- you know, I might have that.

DR. JANOSKY: Because it would be reasonable for me to think it was a 70-30 split like there was in the patient recruitment, but that might be unfair to just come to that

conclusion.

DR. MULRY: Mary, would you have that?

DR. JANOSKY: Was the sponsor able to get that piece of information?

It is exactly 70-30. Okay.

While they're just confirming that, let me raise one other issue with you. Maybe you can enlighten me a little bit. I see the two instruments are paper and pencil, and one instrument of the outcomes is face to face. The patient needs to be there.

The sponsor gave the discussion that perhaps they didn't have complete data for all of those follow-up because either the patients were doing well so that it didn't come back or geographically they were at such a distance they didn't want to make the trip, et cetera, et cetera, et cetera.

If I go with that second hypothesis that they had postulated, which was the patients are at such a distance they didn't want to come back, confirming that hypothesis for me would be that they would at least have two of those assessments done per patient. In that they would have said, "Okay. You're not willing to come back, but will you please complete these VAS for us because those are patient self-report?"

Do you have any indication that that was done, that they have missing data depending on type of outcome?

DR. MULRY: I don't think there was enough information in the application to tell us one way or the other whether they did that.

DR. JANOSKY: Okay. So it's not fair for me to necessarily conclude that that second hypothesis, which was geography, was one of the issues that patients didn't return? Because that's a very simple thing to do, ask a patient to complete paper and pencil.

DR. MULRY: I don't think there's enough information in there for us to make that determination. We really have to depend on the sponsor to let you know what they actually did in a collection of data.

DR. JANOSKY: Based on your experience with these types of studies, would you expect to see those types of data?

DR. RUNNER: I think with our experience we ask sponsors to get data in any way they can to follow patients.

DR. JANOSKY: Based on my experience I have the same experience, whether that means partial records or not partial records.

Does the sponsor have -- is it a 70-30 split for

that n equals 45 at three years?

We're still searching. Okay. I'll wait a while longer then. Thank you.

DR. JANOSKY: I'd like to follow up with that question and ask the 11 patients that were treated with noncemented. What was the distribution as well?

Are there any other questions from the panel? Ms. Howe.

MS. HOWE: Elizabeth Howe.

Dr. Mulry, my question has to do with your question to us, 6(b), about training. Was there any material given to you to review regarding proposed training that would go along with this product?

DR. MULRY: Not in the clinical section, no.

MS. HOWE: Is there anything available from the sponsor that would show an intent to do a training component?

MS. BLACKWELL: We were told that they were planning to have training for everyone before they were allowed to place the device, and I believe a video was made, but we haven't seen it yet. We usually do labeling and real detailed work after the panel meeting simply because of the time issue.

MS. HOWE: Thank you.

CHAIRMAN HEFFEZ: Mr. Mulry, I have a question for you. In reviewing the indications, many times the patients had multiple diagnoses. Was any attempt made to your knowledge to find a primary diagnosis so that it could be a little bit clearer what the indications were for this surgery?

DR. MULRY: Not that I'm aware of.

CHAIRMAN HEFFEZ: I'll ask the sponsor if they made an attempt to find a primary diagnosis. I'll address it to Dr. Quinn.

For example, some of them have traumatic arthritis, deformity, and several diagnoses, and they're all tallied as that. Is there one table that can tell us what a primary diagnosis is because clearly many of those have secondary diagnoses.

DR. QUINN: Well, we didn't make an attempt to identify one as primary. I'm not sure of the multivariate analysis, whether they were broken. My knowledge is that they weren't. We didn't list one as the primary.

Mary, do we have the data that Dr. Janosky is requesting?

MS. VERSTYNEN: Mary Verstynen.

I have the data for the cohort imputed group of 59 where 41 of the 59, which is 70 percent, were Dr. Quinn's and 18,

which is 31 or 30 percent, for Dr. Sinn. So it was a 70-30 split, and there's no reason to believe that it wasn't the same for the 45 number.

CHAIRMAN HEFFEZ: How about the 11, the cemented 11? Do you know what the distribution is?

MS. VERSTYNEN: It would obviously be more of Dr. Quinn's because Dr. Quinn had 31 of the 38 and Dr. Sinn only cemented seven cases, but I don't know exactly of the 11 how many were Dr. Quinn's and how many were Dr. Sinn's.

CHAIRMAN HEFFEZ: And as far as -- while you're up there, as far as the diagnosis distribution, is that data available to be able to break it down into primary diagnosis?

MS. VERSTYNEN: No. I remember discussing this early on in the protocol, and it seemed to be very difficult to put a primary diagnosis on these patients because of the multiple diagnosis that most of them had. So there's no way to go back and collect it unless we ask for it retrospectively.

CHAIRMAN HEFFEZ: And for the panel, can you define traumatic arthritis, and could you define aseptic necrosis?

MS. VERSTYNEN: I think I'll defer to a clinician on that one.

CHAIRMAN HEFFEZ: Okay.

DR. QUINN: I think the difficulty of the diagnosis question in general is that the patient presents with signs of late stage degeneration and ankylosis. Which one is primary and which one is secondary?

We defined traumatic arthritis as when there was in the preoperative form an identifiable event, when the patient said, "On February 11th, 2000, I was in a motor vehicle accident with direct facial trauma. Prior to that I had no symptoms."

Then we labeled the degenerative changes as traumatic osteoarthritis as opposed. So it's purely labeling by history.

CHAIRMAN HEFFEZ: And aseptic necrosis, how did you define that?

DR. QUINN: Well, aseptic necrosis and avascular necrosis, as you know, is a hot topic in the temporomandibular joint literature. If there was imaging evidence where avascular necrosis was mentioned as part of the imaging, I'm not a believer that the avascular necrosis is as prevalent in the temporomandibular joint as in other joints, but if the imaging prior to surgery mentioned avascular necrosis or aseptic necrosis, we use the term based on the radiologic evidence.

CHAIRMAN HEFFEZ: So it was based on the

radiologist's diagnosis?

DR. QUINN: Yes.

CHAIRMAN HEFFEZ: Okay. Excuse me. Dr. Bertrand.

DR. BERTRAND: Peter Bertrand, a question for Dr. Mulry.

You've charged us with understanding whether or not the three-year data is reflective of the rest of the patient group.

DR. MULRY: Yes, sir.

DR. BERTRAND: That may very well be true at three years with the others for pain, chewing ability, and incisal opening. My concern though is how is the three-year implant arrived at. Why not six years? And why that three years may not be sufficient time to see any type of immune reactions manifested in the patient group.

DR. RUNNER: I think -- this is Susan Runner -- I'm going to answer that question. We developed a guidance document with input from clinicians some years ago that stated that for temporomandibular joint implants there would be a three-year cutoff for data. That was arrived at with input from the various people.

Obviously you could continue out patients for a long period of time to get additional data, but that has been the standard.

It has also been a primary standard in orthopedic studies as well.

DR. BERTRAND: I'm going to expose my immunologic ignorance here, but for my own edification maybe anybody can help me understand it. Is three years sufficient time to explore the possibility of immune functions, especially if there's some material failure at four, five, six, and seven years?

I don't know if anybody can shed any light on that.

CHAIRMAN HEFFEZ: Dr. Li.

DR. LI: Well, I can give an answer from a total knee side that three years would be an extraordinarily short time to see any immune response to polyethylene or metal debris. The wear rate would have to be horrendous for it to show up in three years.

But a bad or high wear rate would probably take a minimum of five to seven years before you saw the immunological response. So if you had -- so unless the wear rate was horrendous, which does not appear to be in this case, the wear rate still could be high enough to cause a response at five, which would be invisible at three if it was a total hip or a knee.

DR. BERTRAND: So a question for Susan Runner then. Was there consultation with people concerning reactions where

a three-year time frame was developed?

DR. RUNNER: I don't believe that's the case.

DR. BERTRAND: Thank you.

CHAIRMAN HEFFEZ: Dr. Suzuki.

DR. SUZUKI: Jon Suzuki.

A question for Dr. Mulry really. With respect to the determining what the learning curve is on implanting these devices, is there a way that the panel can look at either the rate at which the devices had to be removed or the morbidity that occurred as the surgeon gave experience?

The reason I'm asking this question about the learning curve is that it may impact on answering like training issues and whether or not these two sites are acceptable.

DR. MULRY: I think all of those could be factored in. I think it would be helpful if we heard maybe from Dr. Quinn who has been training the other surgeons for this technique as to what value it's had and what they've had to do in the process of training, along with the other information.

DR. QUINN: I think it's an excellent point. I don't think we saw any glaring differences based on the curve, but I think Dr. Sinn and I would be considered relatively experienced surgeons.

I think it is an issue, and I think it's not only an issue in this device, but if you look at the leap frog initiatives in this country that they're looking at a minimum number of procedures in a lot of things like open heart surgery and angioplasties, and so I would apply the same logic to this device, that hopefully it will be done by surgeons and centers where there's a minimum amount that would determine that expertise.

I don't know what that is. Remember we're starting with a small number, to begin with, and I think we have to keep that in consideration. Our plan is to have any surgeon who is going to implant this device train by either Dr. Sinn or myself and then move to a train the trainer mode.

They would also have to take a course, and that's part of the videotape that's being developed. I feel very strongly that someone who has no background in this surgery shouldn't make the hyper leap into placing a total joint prosthesis, but I think you can use the same logic in any advanced reconstructive procedure in the orthopedic world as well.

CHAIRMAN HEFFEZ: Okay, and we'll just have two additional questions. Ms. Helms and then Dr. Burton, and then we'll move on to the reviewers.

MS. HELMS: Thank you.

Elizabeth Helms.

I have a question for Dr. Quinn on number three and a question for Dr. Mulry on number six.

Of the 52 patients that had the adverse effects, do you know what their quality of life is to date? And were any of those 52 incorporated into the end of the three-year trial in that information of the outcomes?

DR. QUINN: I think the pat. key that identifies every patient and also identifies the adverse events, I could link them to them. I'm not sure I could give you a comprehensive listing.

When you say quality of life in terms of the parameters we followed or something beyond that?

MS. HELMS: Right. The pain, for one.

DR. QUINN: Well, actually we could link the adverse events to specific patients and look at the data. I'm not sure I could recite it for you.

DR. RUNNER: Well, excuse me, but didn't all 52, except for the eight removed, didn't they go on to resolve their adverse events and become successes?

DR. QUINN: Except for the eight, yes.

MS. HELMS: Except for the eight. Right, okay.

DR. QUINN: And what was the second part of the

question?

MS. HELMS: The second part of the question is number six. On the labeling, the disclosure information, is there significant disclosure information in the labeling for consumers to understand what is being implanted?

DR. RUNNER: Susan Runner.

The company has provided the patient labeling, and that has been reviewed by our Office of Health Industry Programs, and it's inconsistent with other TMJ implant patient labeling materials.

CHAIRMAN HEFFEZ: Okay. Dr. Burton.

DR. BURTON: Richard Burton, and this could either go to Dr. Mulry or to Dr. Quinn.

One thing, we've talked about some wear issues, and they've talked about whether fatigue testing and how long it would last and things, but has anyone at least even -- I always say this, "venture to guess" -- but what is the expected life expectancy that you informed the patient of?

I looked at the patient literature, and it doesn't really address that, and obviously you're dealing if you're looking at the demographics with a reasonably young population. You know, if you have a device that can last whether it's five years or ten

years or 15 years and you have a 30 year old patient, and these are multiply operated patients, what then is the future that they're looking at as well?

And I mean, I think that the patient needs to at least I don't know whether it's publish or not, but it needs to at least have some concept of: fine, I'm 30 years old. I'm getting this joint implant. Hopefully this will improve my pain and function, but what is my long-term expectancy with this?

I know what we tell patients and knowing some orthopedic colleagues what they tell them. You know, if you're X years old and you get a knee done, you know, this is what you can reasonably expect. This is what you can expect from your hip. What can I expect from this implant in terms of a life expectancy?

And obviously there is a range, and at this juncture obviously given the time frame out, somewhat obviously speculative.

DR. MULRY: Yeah, I'm not sure I can answer that from looking at the clinical data because the data is only out to six years, and I think that was five patients. So we really don't have anything beyond that to draw upon in terms of data.

So maybe Dr. Quinn or one of the engineers may be able to answer that.

DR. QUINN: It's an excellent question because every

patient who has this asks me that question, and in honesty you have to say, "I can only tell you the longest one out is six years and one month."

I'm not sure there is a method, and if the statistician could help me to say if 59 of them are out four years, I can impute that they would last a range. I don't know whether you can do that, but my experience with the most recent stock implant that we used in over a period of 12 years, implanted a good number of them, the average life span was about six and a half years where we started to see -- but we saw significant, to get to Dr. Li's point, polymeric debris where the current episodic swelling, loosening much earlier in the use of that device.

And I may have to defer to Dr. Runner, but my understanding was in 1994 during this initial submission, there was a definition that five years was a reasonable expectation from the temporomandibular joint device. I think that was the arbitrary definition at the beginning of this process, and if anyone can comment beyond that, I would appreciate it.

DR. RUNNER: I believe that was the --

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I'm sorry.

I believe that was the idea behind the ten million

cycles with an estimate of two million cycles per year as an estimate. I believe that's what went into that number for the fatigue testing.

DR. QUINN: I think the variability here is, as you know, that I thought the latest wear testing I saw was in the normal adult joint you would have 13 million functioning rotations in a ten-year period.

The problem is that variability in this case because in the normal patient, your teeth are in contact 18 to 24 hours a day, and a bruxer can be up to four hours. So I think there's a huge variability in there.

CHAIRMAN HEFFEZ: One of the problems, you say in six years the other type of prosthesis demonstrated metallosis and problems, and yet we didn't study very well the microscopic debris here, and we're not at six years with this device. So I think you have to just fill in and paint the picture a little bit better.

DR. QUINN: Well, I'm comparing a device that largely had a methyl methacrylate head, and wear testing is grossly different than a cobalt chrome head against polyethylene. So I think that -- is that the point?

CHAIRMAN HEFFEZ: Well, it goes back to Dr. Li's

point where how much of the testing has been done from a microscopic point of view to demonstrate the wear.

DR. QUINN: I should mention that we did do testing against what we referred to as the predicate device as part of the submission, and we did use five of the devices that I was referring to and compared them, and we do have that data if it would be helpful.

CHAIRMAN HEFFEZ: This data would be representing five in vitro testing?

DR. QUINN: I may ask Shawn to help me.

We did test the Lorenz TMJ device against what we referred to as the predicate device.

CHAIRMAN HEFFEZ: We can't --

DR. RUNNER: I think for PMAs, PMAs have to stand on their own.

CHAIRMAN HEFFEZ: Right.

DR. RUNNER: We don't really compare to previous devices.

CHAIRMAN HEFFEZ: Okay. Thank you.

I would like to move forward with the primary reviewers. There will be three primary reviewers: Dr. Rekow, Dr. Burton and Dr. Janosky, and we'll go in that order. I'll allot

15 minutes maximum for each one, to be followed with five questions.

Dr. Rekow.

DR. REKOW: Well, I won't use up my 15 minutes.

I think that there are a couple of important points to make. I think that the corporate issues have made it a point to address the ASTM and ISO standards, and I think that most of the testing that was done and proposed follows issues that were completed before the IDE submission, and I think that -- is that a proper statement, Susan?

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: The testing was approved with the IDE, but before the PMA submission.

DR. REKOW: Right, and so much of this has been reviewed before. And so I think that we need to keep that history in perspective.

Well, we still need to address the issues of the safety and efficacy, but we do need to identify that much of this testing was done some time ago.

In my opinion, as I looked at the different designs as I understood them from the drawings and the information that was presented to us, there has certainly been an evolution in the designs, but from my assessment those typically have not changed

minimum thicknesses, nor have they made radical changes in areas that would be the most likely high stress concentration areas.

So I think that the tests that have been done, while there have been changes in the design, don't remarkably change the anticipated results, with perhaps the small exception of the pre- and post peg question, and that is being addressed now.

I have a small concern about whether or not the test that was originally designed, where you don't have a compliance substructure to adequately give you the failure mechanisms under fatigue loading, but indeed, they are providing information that will be able to be correlated with the historical testing, and so it's an interesting question about which of those is the most appropriate approach to take.

A couple of other concerns that I think may need to be addressed as part of our concern is some of the testing was done with bovine bone thicknesses. I believe that was the pull-up test. No. Was that the pull-up test that was done?

And there the cortical plate was argued to be twice as thick as the cortical plate in the mandible, but you would put your screws through both sides of the mandible.

And if that's true that you really go through the whole cortical plate on both sides of the mandible, it's a good

argument. The question is how much of the second side of the cortical plate the mandible gets engaged in the screws. I think that that's not a critical issue. I think it's one that just needs to be addressed, needs to be thought about a little bit.

I am slightly concerned with some of the issues that Dr. Li has brought up about the creep in the fossa component, and more particularly about the wear debris and the scenario of the wear debris because that historically has been such a remarkable issue.

I would encourage you to look at the wear debris with your new testing and to do it rather aggressively, and if you find things perhaps you might want to propose some other testing be done to either allay fears or to change your design.

I think though that it's also important to note that these are the materials that are being used in other applications, and they have succeeded in other clinical applications. So I don't think that the concerns that I'm raising should be alarmist concerns, but I do think that we need to know a little bit more about the wear debris and its outcomes because that to me is a singular issue that could potentially create some very difficult in vivo problems.

CHAIRMAN HEFFEZ: Any questions to Dr. Rekow from

the panel?

(No response.)

CHAIRMAN HEFFEZ: Then we'll move to Dr. Burton.

DR. BURTON: Richard Burton.

I'll try to deal just strictly with the clinical issues. Many of these, as of the issues that I found in my review, have already been answered, and I'll just try to sort of maybe perhaps raise them and close some of the questions at the same time.

In reviewing obviously from a clinical standpoint, I looked at the complication rate, which I would agree is certainly within the norms for this type of patient population in my experience. The type of complications which we saw, again, is that we saw there were only eight explanted joints. Most of those result, sometimes not spontaneously but within normal conservative management techniques, and the most common ones being neuromas and various scar tissue adhesion type of issues, which, again, are very common in this type of population.

And as Dr. Quinn pointed out, the issue of heterotopic bone with both TMJ surgery and with any type of implant. Over the years we have seen that to be a constant source of problem, one which at least at this juncture has not had a good answer for

that.

The concern I had in looking at the complication rate is that just sort of anecdotally as I reviewed the entire patient population and the patient key for that, my sort of gut feeling was the fact that there certainly had been somewhat of a decrease in rate as you went further on in the study, which again would play into the fact of experience, time issues, and time of surgery issues, which Dr. Quinn explained as well, and I would certainly make the comment that in having treated patients for a number of years where you had unilateral TMJ problems, that once you improve their primary complaint site, suddenly the site which had not been their primary complaint, oftentimes they would return regardless of the type of procedure that was done in saying, "Gee, this site is really a lot better. Now my other site."

And you know, you raised the question whether or not that was a shift in load. Many of us have asked ourselves that question over the years, and this is certainly within the realm of the possible. Many times, I think, most of us have felt that that was a fact, is that the patient becomes aware of those symptoms. Like most of us, you know, if you have one primary complaint, once that's addressed sometimes you move on to more secondary issues.

Review of the surgical indications I thought were adequately explained because I had some concern regarding the ages with that. I would concur with Dr. Quinn in the fact that I think that avascular necrosis is a vastly overplayed term, which has become sort of a popular catch-all for some unexplained situations, and I think that we've sort of allowed some time to our radiographic colleagues to sort of push us towards that diagnosis where many of us clinically are not quite sure that that exists to that level.

I did have some concerns regarding the issue of site bias and the fact that, again, if you looked at the original protocol and you were talking 300 patients, which I thought was quite laudable, but again, a reasonably large group, in ten sites would have been good.

But again, the point where we have eight surgeries done by three additional sites, I have concerns whether the complication rate that we're currently seeing, which is both reasonable in both the type and the numbers, may be a reflection of the fact of the experience level of those surgeons placing the devices and whether as we expand the number of sites, were this product approved, whether we're going to seek a concomitant increase in the rate of complications.

The change from a clinical standpoint, from a

cemented to a noncemented fossa I think Dr. Quinn addressed, and again, in looking through their surgical guide, they had developed -- did you develop the burr, the burr that you're using, that diamond burr, for fossa contouring? It was specifically designed for that.

Most of us who had used other systems found that that was very problematic, and I think that that's where the need for cement came from. I think that most of us feel, again, any factor you don't have to introduce into that area reduces that, and I guess that's not something that personally I have that change to be much of an issue. I think that that, candidly, an improvement.

My last concerns work primarily around the labeling issues, that we have an adequate review of the labeling and indications for that, and then again, this has been addressed several times as a clinician, the fact that I think this is going to be quite dependent upon having an adequate training program such that it will release into broader use of hands, we'll continue to see what are reasonable clinical outcomes with that.

And then lastly, like I said, just the life span issue, that's very difficult to explain, but every patient's idea with various devices always has to say, "Well, gee, how long is this going to last me?"

Certainly we can't give them that answer, but looking

historically at other issues we need to be able to provide some type of answer to that.

And then from a nonclinical standpoint, I think Dr. Li's question of wear debris because it has been my experience that everything has some wear debris, and again, usually if you're not seeing it, you're just not looking at the right level to find that.

I'll take any questions.

CHAIRMAN HEFFEZ: Any questions? Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Concerning the longevity of the device being implanted and the statement that you made, Dr. Quinn, concerning that most of these patients probably have 18 to 24 hours of tooth contact a day, either pre-surgically or post surgically is any attention given to the ability to control tooth contact?

It's been pretty well established through neural science that one of the strongest brain responses to incoming stimuli is either tongue bracing or tooth touching. Has there been any work done towards addressing that?

Which if you reduce that 18 to 24 hours of tooth contact, it might in the long run improve the longevity of the appliances implanted.

DR. BURTON: I would say that, you know, that's something that possibly could and probably should be addressed. Again, you have the possibility with any type of device that you've taken the patient who certainly has what may be a degenerative joint disease or something else, which is a clinically identifiable pathology, if you want to call it that, who also has underlying neurophysiological issues.

And I think that at least what I get that you're asking is once you made, you know, the surgery deals with the more overt clinical pathology, but then once you have addressed that, should you then turn around and try to address perhaps an underlying neurophysiological issue which in a sort of, you know, which came first, the chicken or the egg, but at that point in time perhaps, yes, they may need -- a person who failed surgical or non-surgical therapy and has a surgery may still be a candidate for some nonsurgical therapy which then may extend the life of their implant.

That would be my sort of professional opinion on it.

DR. BERTRAND: Dr. Quinn, is there any either pre-surgical or post surgical way of addressing that tendency that you made reference to?

DR. QUINN: I actually agree with Dr. Burton. There

is continuing nonsurgical therapy. It doesn't end with the implantation. I think the question is -- and I'm not sure I could answer it -- is the chicken or egg question. Do people brux because they have pain or do they have pain because they brux?

My anecdotal evidence is that if you reduce the pain levels, we do see a reduction. It wasn't a variable we followed, but it would be an interesting one to look at. My impression is that as the pain levels dropped we see less, but we still have people who continue to brux afterwards.

And I think to Dr. Li's point and your point, we will continue to use splints to theoretically unload the joint afterwards, which would theoretically decrease wear, but you know there are patients that no matter what we do, I've seen them brux right down to the pulp of the teeth. They're very difficult problems.

DR. BERTRAND: Thank you.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: So this is Susan Runner.

Dr. Bertrand, are you suggesting that there could be a labeling issue regarding postoperative treatment of these patients in terms of addressing this issue specifically?

DR. BERTRAND: I'm not sure that the use of a

mouthguard is going to actually decrease the amount of loading over time on an appliance that has been surgically implanted. I think the way any type of cranial nerve mediated motor reaction occurs is neurochemically facilitated by incoming stimuli, but there are emerging ways to address that that is coming out in neuroscience which might enhance the longevity of any type of device placed into an area of the body that's controlled by cranial nerve reactions.

CHAIRMAN HEFFEZ: Dr. Schechter.

DR. SCHECHTER: Dan Schechter.

Dr. Burton, with respect to your concern about the number of sites and potential bias in there, how comfortable or what is your opinion with the sponsor's response regarding the population of available patients and available surgeons with appropriate patients?

DR. BURTON: I think that they're attempting, you know, to address that topic. My concern is a surgeon, and I'm one, you know, that exists in a, you know, university training environment where, again, we tend to see -- you know, there are certain procedures where we do -- and we're probably the only people in our state, and being a sparsely populated state that performed those, is that this appears to be something at least from what

Dr. Quinn was saying is probably more appropriate in a limited number of sites, hopefully more scattered about the country.

And I mean, that's not something we or I should say that I think that the FDA controls, but I think that you have to have some assurances that there is going to be an adequate training level because we have seen, looking back historically not only in oral surgery, but in certainly other areas that things work very well in certain surgeon's hands, and sometimes those are the individuals that develop that they have both the expertise and the experience to do that when, unfortunately, both devices and techniques get into less experienced hands.

You suddenly discover that complications that nobody dreamed of suddenly start to come out again, and we see other adverse effects and adverse outcomes from that, and again, you know, certainly the sponsor of the company can't guarantee that, but I think that as much as they can address that educational issue and how the devices are released to other surgeons at least can be examined.

And I think they've tried to address that, but that's my biggest concern, is when you have things that work well in certain people's hands and certain levels of experience that doesn't translate well to the general population of providers and

practitioners that are out there.

CHAIRMAN HEFFEZ: I'd like to move on to the next reviewer. Dr. Janosky.

DR. JANOSKY: Janine Janosky.

I have four primary issues that I wanted to spend some time talking about and discussing, and they are the issues that I primarily have been spending time talking about this morning also, as well as some other panel members have been talking about.

The number one issue is the issue of follow-up. If we look at the primary outcome measure, the primary outcome measure is a three-year measurement, and irrespective of how we measure that, we come down to about 45 people, and of those 45 people, you have 11 of them that are noncemented. So you even have a subset of the 45 that is quite small, and that's actually that noncemented group is about ten percent of those that had started the study. The 45 is about 25 percent of those that have started the study.

So the issue then becomes: for primary outcome measures is 25 percent follow-up acceptable? Depending upon what criterion we will use, for the most part we would conclude that that would not be an acceptable level.

So then the issue becomes why is the follow-up so

low. Revolving enrollment, that's understandable, but then why are we looking at the PMA today as opposed to when most of that enrollment would be?

Some of the issues to try to get at why the enrollment was or why the follow-up is so small I tried to deal with in terms of hypotheses that the sponsor had presented to us, and one of those issues is: could you get some of the outcome measures, but not all of the outcome measures, given the fact that two of the outcome measures are paper and pencil, and we could ask the patients to respond on the VAS scales and send them back to their provider.

And the answer was that we don't have missing data irrespective of the type, and so there's some confusion as to whether there was, there wasn't. But I had taken a look at the data and the spreadsheet that was presented to us, and if someone is missing one of those measurements, they're missing all three of those measurements.

So that raises some concern to me as to why weren't they at least given the opportunity to provide the data for those that they can do using mail.

So the issue of follow-up, it encompasses all these other issues that I'm talking about, but for an event of 45 for three-year follow-up, which represents 25 percent, is that

reasonable or is that not reasonable?

The second issue is the one that we had just started talking about when Dr. Bertrand had brought it up and the one that we had talked about this morning, is that we're looking at two clinical sites, and I find it quite interesting that the sponsor refers to this as an efficacy study, which I would argue with two clinical sites it is, in fact, an efficacy study.

But we're not talking about efficacy when we're looking at the FDA. We're talking about effectiveness. So the question of whether two clinical sites with one practitioner at each of those sites is an issue for efficacy which is not our concern here or is it an issue of effectiveness which is our concern?

And the issue of whether it's an issue of effectiveness, I think, has been addressed by most of the panel members and leading in one direction.

The third issue is the one about outcomes, which we had talked about when I had talked about follow-up, and the final one is a pure statistical question which I had raised to the biostatistician at FDA in that the statistical assumptions are most likely not met for the statistical techniques that were done.

So then the question arises: would you have gotten

the same conclusions if you had used the appropriate statistical test?

I don't know the answer to that because the sponsor didn't provide the data analyses analyzed using other statistical techniques. So I'm left with as much confusion as I had this morning. I was hoping to get some feedback from the sponsor and from some other panel members as to how we deal with some of these issues and how we think through some of the issues.

So, again, the issues are the follow-up, the site selection, and the practitioners, one at each of the sites.

The outcome measures and why we don't have inconsistency in terms of that, why were the patients not given the opportunity to fulfill at least the paper and pencil assessments, and then the final one which is a purely statistical analytical question.

I'll stop at that point.

CHAIRMAN HEFFEZ: Thank you. Thank you, Dr. Janosky.

Dr. Li.

DR. LI: You're right. You may have already answered this in a previous discussion, but I might have missed it. How long did you estimate or did someone estimate it would take for you to get to 80 percent of 180 cases to reach three years?

DR. JANOSKY: Yeah. If I take a look at 180, and we can deal with that issue of cases versus sides versus patients, but let's just give them the opportunity to say that cases is 180.

If you take 80 percent of 180, you get 144, and then have 143 measurements at six months.

DR. LI: So it takes two and a half years then to get to three years?

DR. JANOSKY: Approximately, right. So 80 percent of their data are available for six months worth of time. So on some level we can argue that there's six months worth of data available.

DR. REKOW: But can I?

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: Can I just go back? I agree with everything that you've said, but I also heard that the initial study was planned for only 68 patients, and I think we need to make sure we know what is the real basis that we're supposed to be using as our basis, and I don't know the answer, and it looks like Susan is anxious to tell us.

DR. RUNNER: Susan Runner.

I believe it was 89 -- 86. The initial IDE was approved with a projected number of 86, and that's the number that

the original statistics were based on.

DR. REKOW: And that was to be 86 patients with three years' worth of --

DR. RUNNER: Correct.

DR. REKOW: Eighty-six cases or 86 patients?

DR. RUNNER: I believe when we sent an IDE letter, we're talking about 86 patients. I mean, I think they interpreted it a little bit differently and changed it around, but we're talking basically about 86 people.

They then requested expansion of the study, and that's how we got to 300 approved, and they've gotten 180 operated at this point.

DR. JANOSKY: This is Janine Janosky.

I would postulate two things, Dr. Runner and Dr. Rekow, at that point. If that is the case, then what 86 are we going to take?

The sponsor didn't present to us data on only 86. So I would expect to see the first 86 or the 86 meeting inclusion/exclusion criteria, and their data presented separately. That would be the first concern.

The second concern, let's give them the fact that there was 86 and I'm assuming that that was based on statistical

power analyses in terms of estimates.

Then what is 80 percent of 86? That's in the 60s. Do we have data on 60 patients for three years? And the answer is, no, we don't.

So even if you argue that there's 86 in there, that you should have three years' worth of data on and taking an 80 percent rate, 20 percent attrition, you would expect 60-some patients with three years' worth of data, and we don't see those numbers.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Simple question: were 86 people enrolled before January '99? I mean, that would give us a rough three-year follow-up.

How long did it take us to enroll those?

CHAIRMAN HEFFEZ: Would the sponsor come to the podium, please?

MS. VERSTYNEN: Mary Verstynen.

I believe that the first 86 patients enrolled will be out to three years in October of this year.

DR. BERTRAND: So it wasn't by January '99, January 2002 that you had 86 people originally enrolled. It took longer

than '99 to get that many in.

MS. VERSTYNEN: Right, and so it would have been in October of '99 that we had the 86 patients enrolled, and they would be at three years.

DR. BERTRAND: So in three months?

MS. VERSTYNEN: Yes.

DR. BERTRAND: Okay. So from that standpoint with 45, is there a way of figuring out how many of those 45 -- what date they were originally enrolled so that we could get an idea on that concept.

MS. VERSTYNEN: I can tell you in the first year of the study nine patients were enrolled, and then the study was enrollment stopped for a year's time period just to follow those first nine patients. So there was a real lag in the enrollment initially.

So I would say it probably took us -- I don't know that I could put an exact date, but enrollment started out very slow and has built tremendously in the last two years, and it actually built -- now, Dr. Sinn's patients first were at three years. I believe was it in -- I remember. I remember he did it at Easter time. It was April '99. Was that when?

Did your first patients come out to three years this

year or last year? Do you remember?

This year. Okay. So enroll really built then in April of 1999 when Dr. Sinn was added to the study.

DR. BERTRAND: So a lot more patients have been recruited since '99 than previously?

MS. VERSTYNEN: Yes, yes.

DR. BERTRAND: Okay.

MS. VERSTYNEN: I also want to state, too, as far as the sample size calculation that was originally in the IDE. Phyllis Silverman, we had worked with her in getting that sample size calculation, and at that point, looking at the literature, the outcome -- the delta of that calculation was based on a one centimeter improvement in pain, and clearly we see much more than that at the three-year time point.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: I guess my question, I guess, that Dr. Janosky -- at least what I have summarized in my mind what she's asking though is that given the fact that there appear to be an endpoint of when we would reach that number and we would have the three-year data for what was thought to be the original power or patient's number of studies, and we don't seem to be there, what prompted them?

If it was going to be in October of this year, we would reach that number. Why is it August and we're at that point?

And maybe Dr. Runner can answer that. What prompted the timing issue with this coming forward to the panel?

DR. RUNNER: I think the company needs to answer that question.

MS. VERSTYNEN: I can tell you exactly when that question was answered. It was at the last panel meeting in 2000, and at that point, both FDA and a Canadian official were there, and I had printed out the proposed follow-up that we would have in the next couple of years.

Knowing that we had predetermined a cutoff of 86, I just showed them, okay, at this point we're going to have this many patients. At this point we'll have this many patients. At this point we'll have this many patients, and both FDA and the Canadian official said that when we had reached I think it was 49 patients at three years, that that would be an appropriate time to submit it.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky.

Ms. Verstynen, the number 49, what was that based on, the one that you just quoted, the number 49?

MS. VERSTYNEN: I went into our database and I picked, okay, cases that were done in a certain date. I just went back to the surgery dates just to see, okay, how many would I have at this time point. How many would I have at this time point?

DR. JANOSKY: Let me stop you for a second.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky.

DR. RUNNER: Can I just make one comment? And correct me if I'm wrong, Mary. I know PMAs are supposed to stand on their own, and I believe that -- and you correct me if I'm wrong -- that your desire to comment came about because of the history of the numbers that were associated with the two previous PMAs.

MS. VERSTYNEN: Exactly. I mean, I guess I was proposing and figuring out how many patients we had had at different time frames, and looking and having been at the two other panel meetings, our number that FDA and the Canadian office set of 40 was far higher than the approved products.

DR. JANOSKY: Let me just follow up, please.

Janine Janosky.

Ms. Verstynen, typically we stopped studies based on criterion or criteria, depending upon how many we have, objective stopping rules so that if something is very effective, we might

stop it early because we can argue that we see much larger the effect that we possibly said.

So your number that you just said to us, that was not based on a specific stopping order; is that correct?

MS. VERSTYNEN: Correct.

Thank you.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

A question for Dr. Janosky. You've used the number 80 percent on several occasions, and I assume that that number is a number that one seeks in a clinical trial, but is that number necessarily fair given the nature of this trial, the nature of the patients, the nature of the multiple surgeries, and the psychological implications that go with patients suffering from this level of dysfunction? Is that fair to apply that number to this study?

DR. JANOSKY: I used the number based on a couple of things. One is typically what is the response level that we expect to see.

The second, always if we're estimating a point, how many subjects do we need for a point estimation? So if we're looking at a specific type of confidence interval for a point estimation,

how many subjects would we need based on a level?

So I'm sort of backtracking and giving them the benefit of the doubt.

DR. PATTERS: Let me then ask if --

DR. JANOSKY: So I actually would jack it up a little higher is what I'm saying.

DR. PATTERS: If we look at their patient accountability data which they provide on Table 8-7, they say that of the patients available at three years, theoretically available, 82 and a half percent of them are included in the data, which is 45.

If we go back for a year and a half, 89 of the theoretically possible 109 are available in the data. So if we assume that their losses don't change, you know, about roughly about 82 and a half percent of the patients are available. That would mean that we'd have approximately 85 patients available within a year and a half.

Would you read that the way I'm reading it?

DR. JANOSKY: I would probably come to the same estimates, although those are only estimates.

This is Janine Janosky speaking.

DR. BURTON: Yes, I understand that, but regardless

of how many they started with, 85 patients are a lot of patients for what they're doing. It may be only 50 percent of what they started, but it's a lot of patients.

Do you take that into account?

DR. JANOSKY: This is Janine Janosky again.

If you're going to argue that 50 percent is reasonable, then I would want to see data that shows me that those 50 percent that completed were no different than the 50 percent that did not complete. I don't see those data.

So when I don't see data that I expect to see and I don't see a fair amount of data that I do expect to see, I need to wonder why. And since I don't have any basis to base anything on, say, okay, give me some hypotheses why I don't see this. Then I have to conclude that I don't know the answer.

So I can't conclude that 50 percent would be reasonable. So that's the quandary that I'm left with.

CHAIRMAN HEFFEZ: Dr. Burton?

DR. BURTON: I'm not sure this goes to Dr. Janosky or actually back to the sponsor, but in looking through this, it did state that you were starting marketing in Europe and obviously the PMA needs to stay and the IDE stands upon its own merits here, but also you've been marketing this device for at least greater

than two years.

And I notice I've been reading. It was in South Africa. Do you have any supporting or correlating data from its usage in areas outside the country or at least any comment upon that?

Because it's interesting. I just thought it was done and there's nothing saying numbers sold. Has there been with potentially less experienced people -- have you seen any other issues raised with that?

Because, again, I saw that at least that is occurring, but there is no reference beyond the fact that it is occurring.

DR. QUINN: Based on the Canadian approval and the CE approval, I have trained three surgeons, one in London, one in Sweden, and one in Toronto, who are well know, well experienced surgeons. I think the total number of cases among those three is approximately 75.

I don't have data on it, but that's the number of cases that's been done.

Might I comment on some of Dr. Janosky's? I think a few issues.

One, I appreciate your comment on partial data, and

maybe it was my assumption that since these follow-up visits were radiological and face to face, that was maybe my misinterpretation that we weren't looking for partial data, and we either got data or we didn't.

I think there's about nine patients who actually were seen by an oral surgeon in another part of the country who did the face to face, did the X-rays, and we accepted that. I did not pursue your concept of partial data, which may have been helpful.

The other one is in looking at the -- and I know you questioned the term "efficacy" -- but in looking at the three primary efficacy points that we looked at, we did feel strongly that the data does tend to plateau between three and six months, and we were hoping that would be taken into consideration when looking at the percent of follow-up at three years; that they would be similar.

It may not address the issues Dr. Li raised, and I think they're important ones, but in terms of the efficacy or whatever term you'd like to use, I do think that's an important factor to take into consideration.

The other one in terms of early in the study of broadening this to multiple investigators and multiple sites, it

was probably my reticence that stopped the company. I had some severe reservations. I think it was difficult enough to control this in a very controlled environment. I think it would have been more difficult because, as Dr. Rekow said, there was an evolution. There were no events in this process, but it was an evolution, and I think that evolution was better controlled in a smaller environment.

CHAIRMAN HEFFEZ: Sometimes in studies such as this, data obtained from smaller sites is actually more valuable than data from bigger sites because you get to appreciate different indications, different surgeons' abilities, and that might end up sometimes judging the final usage, you know, of the instrument.

CHAIRMAN HEFFEZ: Any other questions? Dr. Li.

DR. LI: Can I -- Steve Li -- can I switch gears and ask a materials and mechanics question?

One question I forgot to ask earlier, you're using titanium screws on a cobalt chrome plate. In total joints we tried to list the last several years avoiding mixed metal contract because of crevice corrosion. For instance, we put a cobalt chrome head and a titanium stem. You'll actually find corrosion at the interface.

So my question is: do you see corrosion in these

locations of mixed metal contact or, better yet, have you actually looked for corrosion at any point where the mixed metals are in contact?

MR. ROMAN: I can't answer that question from a clinical standpoint. I have not visually seen any of the explants. It might be something that Dr. Quinn can answer.

But as far as looking for corrosion at an interface between the titanium and the cobalt chrome, that's not something that we've looked specifically for.

I did want to say however, that we are using the or that the titanium plasma spray coating that's on the mandibular components is also a Titanium 64 alloy, and we have quite a bit of experience with this in the orthopedic realm and have seen no problems with that.

DR. REKOW: This is Dr. Rekow.

Do you plasma spray the inside of the screw holes on the mandibular implant?

MR. ROMAN: No, no. It's limited to the ramal side of the plate.

DR. LI: Steve Li.

I would just suggest that you might want to look though where the screw holes and the screws interface because the

crevice corrosion is often dictated by the size of the space and the local pH. So it's quite possible on your coating the crevices are of a certain size where you won't get corrosion, but if you switch the joint space, if you will, around the mixed metals, you could get into an area where corrosion is possible.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: This is Dr. Rekow.

Dr. Quinn, can I ask you and Dr. Sinn a question, please? When you do any of the tissue revisions in the joint space for whatever reason, do you as a matter of routine look at those histologically and immunologically, look for immunologic responses?

I know that that's an extra procedure. I know it's a lot of extra work, and I'm just wondering if you're doing that or not as a way to tease out whether or not you're getting any debris particles that could be an issue.

Because with some of your adverse events you're clearly going back into the joint space.

DR. QUINN: I think that has responded to Dr. Li's question this morning. We're doing histologic, standard histologic H&E staining. We haven't done specific immunologic testing, but I think it's not a bad idea.

But I should say coming from a macroscopic point of view, what we tend to see is fibrous encapsulation. It looks like a healthy fibrous glistening encapsulation. We haven't seen multinucleated giant cells or any evidence of polymeric debris, which would be consistent with polyethylene debris as well.

Again, the only foreign body reaction we did get, and it wasn't done, was the corn starch.

There was one other question that I thought you raised and that I'd like to answer, and that was the difference between testing the bovine bone and testing on the human ramus.

We used 2.7 millimeter screws to secure the ramus. They come in eight and ten millimeters, and usually ten millimeters is beyond the bicortical width of the ramus. If anything, we have to back out a ten and put an eight in.

You can actually palpate when the tip of the screw comes through immediately. So in most cases we know we're engaging bicortical bone.

DR. REKOW: Thank you.

CHAIRMAN HEFFEZ: I actually would like to move on to the questions, and when the questions are discussed, I'm sure some of these issues will be revisited.

So all of the questions that are going to be asked to the panel are in your agenda book. We'll try to get it on Power Point so you'll appreciate the question, but it's in your agenda book.

The first question was or is: can the results for jaw pain intensity, interference with eating, and maximum incisal opening for the cases presented with three-year data, which represent 25 percent of the implanted population, adequately represent the expected outcomes for the total study group at three years?

Within this question, I think I'd like to ask the panel to consider that we're talking about cemented and noncemented cases. We have 11 noncemented cases at three years, but at this point in time the experienced surgeons are only placing noncemented prostheses.

We'll have to ask ourselves is the cement an important variable, and is it -- it may not be an important variable, and it is a variable that is now excluded in the noncement cases, and that could be a positive thing.

So I'd like to hear from the panel members how they feel regarding this question.

Dr. Hewlett?

DR. HEWLETT: Actually related to this question I'd like to pose a question to Dr. Li if I could.

Dr. Li, you raised some concerns earlier about the creep or potential creep around the screw holes in the fossa component. My question is twofold.

One, if as the sponsor has described a superior part of the fossa is routinely abutted against temporal bone, does that then lessen your concern about potential creep around the screw holes?

And, number two, do you feel that obduration of any potential dead space with the polymethyl methacrylate cement and thereby perhaps an increased surface area of contact between the superior part of the fossa and the temporary bone, would that then further limit any possible creep around the screw holes in your opinion?

DR. LI: Well, I think the fact that it's supported superiorally helps, but the screws -- and I guess a minimum of four screws -- are placed because they're obviously felt that they're needed to hold the polyethylene in place.

But if there's no load on those screws, you then don't need screws, right? And the fact that you need a minimum of four tells me that either through empirical or through

calculations, that they figure they have needed four screws to hold that polyethylene staple in place.

So that tells me that that polyethylene left to itself is going to want to move away from the bone. Otherwise you wouldn't need four screws.

Now, stress obviously is lower the more supported the polyethylene is, but it clearly isn't zero because there is four or maybe five screws. So I don't think that removes my concern about the creep, although the more supported it is maybe the longer it will take for the creep to get to a level of where you'll cause a problem.

I'm sorry. What was the second part of the question?

DR. HEWLETT: Well, the other part is do you think there's a substantial benefit to using the cement inasmuch as it will increase the surface area contact between fossa element and the temporal bone.

DR. LI: Assuming that the gap or the space is -- there really isn't like a whole gap where the whole back is, you know, unsupported, and they're just like little pockets of unsupported area.

The one saving grace about polyethylene, in fact, is that it does creep and deform. So even if you didn't use bone

cement, after a while the polyethylene I would suspect would kind of settle in eventually and kind of support itself.

So unless the gap is substantially large, I don't in my mind see why you would want to put cement in other than it looks better than it appears to be supported, which leads me to I don't have a great concern over the issue of whether or not the post was clipped off or not clipped off, unless you're going to think you're damaging the polyethylene somehow by the clipping.

But biomechanically in this particular application, I don't see a big influence of whether or not there's a post or no post.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Dr. Burton.

I'd like to sort of answer that as well. I would agree with Dr. Li. When I looked at it from looking at it from my clinical experiences, I didn't think that clipping off the post made any difference, and I actually personally from my experience with cement felt that actually the fact that you modified the technique with a surgical burr to seat the fossa more accurately without the need for cement, and I gather from Dr. Quinn what they found was when they adequately contoured the fossa, they had adequate bone contact, and the volume that they were filling was

so small that they were able to eliminate the cement, that I actually very candidly thought that was an improvement.

You know, you say, well, you have the earlier ones with cement versus noncement, and my guess is that probably eliminating the cement actually probably is an improvement unless from what Dr. Li sort of clarified, unless you felt that you needed the cement for support, but, again, adequately contoured to get good approximation it would be supported.

And by eliminating that cement I think you're just candidly just eliminating one more variable. I don't think that the cement itself has any truly saving grace properties that make you want to have it in there.

So my estimation, when I looked at this before coming here and hearing the other comments, was that that actually was an improvement, not a detractor to the change.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

I would reinforce exactly those comments based upon our experience in periodontal surgery as well, using a number of different agents, cements, infurcations. I felt the fact that they did away with that was probably an excellent move on the sponsor's part in keeping it simply and just the components.

Well, the bone is going to react obviously to the trauma of flattening. You're creating an acute wound, and I think that's where you get some of that hypertrophy of the bone tissue. So I think that as it is without it, it's fine. Also the clipping of the post, I feel like that very little influence on the device as well.

CHAIRMAN HEFFEZ: So let us just summarize this point then. We're saying that the data of cemented and uncemented can actually be combined. Is that the general feeling of this panel?

Okay. So let's come back to the question then. Do we feel that the data that's available is adequate, just to summarize the question? The question is up there.

Dr. Patters?

DR. RUNNER: Can I interrupt for just a second? You basically answered question number four. Is that -- you started with number one, but you sort of answered number four.

CHAIRMAN HEFFEZ: Well, question one involves number four. So that's why I brought it. We're still on number one, but --

DR. PATTERS: Let me try to deal with question number one. I feel like using a percent to say this is only 25 percent of the data is not fair to the sponsor. I think the sponsor needs

to be complimented on conducting what I feel is an obviously scientifically valid clinical trial of which all the data is not presently in.

I think the real issue is are 45 cases at three years enough to conclude safety and effectiveness. I don't know the answer to that, but I don't think it's fair to take a percentage, like 25 percent, and say, well, they've only got a quarter of the data. So it's not enough.

The question is: they have 45 cases now. It appears that they should have 85 cases no less than a year from now, maybe a year and a half from now. How many is enough? I'm not prepared to say, but overall I think that sponsors have taken a very valid scientific approach, and I think they're to be complimented.

It would seem to me that most of the compliments go to Dr. Quinn for conducting what appears to be an excellent and unbiased trial.

CHAIRMAN HEFFEZ: I think we shouldn't focus on the 25 percent, but we still need to answer the question. Do we feel the data that is available at three years is adequate enough to predict an outcome?

Dr. Rekow.

DR. REKOW: This is Dr. Rekow.

I would like to have a little discussion about a little bit different spin on this. When I looked at all of the primary outcome assessments, I didn't see very much change after maybe six months and maybe even shortly after three months.

And so how much new information could we anticipate getting even if there were hundreds of more patients from what seems to be the trend at six months that continues to three years?

And I'd like to hear some conversations about that.

MR. SCHECHTER: This is Dan Schechter.

I know this application is supposed to stand alone, and of course, it does, but as the sponsor noted, similar devices have had less patients involved, and those were approved, and in a sense, if we consider more and more patients, other than the 45 that have already reached the three years, we're in a sense penalizing the sponsor for extending their ID and getting more people involved.

Had they not extended it, the total study group would be much smaller and maybe we would be more willing to just accept the 45. So I think we should keep that in mind that the fact that they're extending this and that very few have gone beyond six months in some sense is a good thing. It means that it has so far been very successful, and FDA is willing to extend that.

But don't penalize the sponsor for that.

MS. HOWE: Elizabeth Howe.

My concern about the number and the amount of data is that there can be additional data collected fairly simplistically; that if we're talking about answers that could be generated by mail or if it could be done at another location and submitted to the researcher there, in fact, is more data out there.

The question is: would those numbers make a difference?

And with such small numbers, it in fact could make a difference.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

You asked the question what more would you gain, and my concern still is obviously Dr. Quinn is a very talented surgeon, and we're thinking about safety issues, and you've got one surgeon who's very gifted with a reasonable number of cases at 30 years, but the additional data I think you're going to get is the variability between surgeons, and clearly when the device is approved, there are going to be a lot of people that use it and hopefully a lot of people wont use it that shouldn't be using

it.

So I think that's where the additional data would come from, is can an average, if you will -- nobody wants to be called "average" -- but an average oral surgeon be able to use this device and have the same results as someone as gifted as Dr. Quinn?

The other is -- I lost my thought. Sorry.

CHAIRMAN HEFFEZ: May I say something? That's really addressing question number two. I think we should just specifically ask if this information that we have now available for three years can give us enough confidence that this outcome will be reproduced in the following years, and that's the biggest question for those issues.

Okay. So Dr. Patters.

DR. PATTERS: Mark Patters.

I'd like to address Dr. Rekow, who I think brought up a very valuable point. It is not necessary in my mind that the sponsor answer these questions at only the three-year data point, and the fact that there seems to be little change in the data after three to six months, to me the panel should consider that information.

As to whether that additional information had

shorter time periods give evidence towards safety and effectiveness, and I think Dr. Rekow's point is an important one and needs to be considered by the panel.

The three years is as arbitrary. It's an arbitrary number that FDA recommended in a guidance document, but that doesn't mean that the data that's not three years old should be ignored.

DR. REKOW: Can I clarify one point? I want to make sure that you --

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: I'm sorry.

I want to make sure that you understand that when I raised that point I was talking about these three parameters of the pain intensity, the eating, and the incisal opening. I clearly think there are some issues related to adverse effects that have other implications.

I wanted to focus the discussion on this from the data that we've seen, and that's where I wanted to have this conversation at this moment to go.

CHAIRMAN HEFFEZ: Dr. Li and then Dr. Burton.

DR. LI: Just a clarification question. For question number one, what are we supposed to consider the total study population?

DR. RUNNER: This is Susan Runner. We consider the total study population the 180 cases that have been implanted.

DR. RUNNER: Thank you.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: In response to that question about the data, I think that for the three presented items I think you probably can because it appears that at that three to six month point that they reach I would say a stable endpoint, but the numbers don't really seem to change.

I think the question is that not having an adequate number out. In looking at previous and other implant systems and other surgical techniques that involve things similar to this, many times we didn't start to see those.

The other problems, other than the pain and opening, started to appear; at least my experience was in that 18 to 36 month point was when you started to see more of the other potential, quote, unquote, complications appear.

So, yes, for those particular outcomes it probably is adequate at this point because I think we can extrapolate that out. The real question is for the overall device. Does that give you the same confidence?

And I'm not sure I have quite the same confidence

for the shortness and the numbers relative to that as I do for those three variables.

CHAIRMAN HEFFEZ: Ms. Helms.

MS. HELMS: Yes, Elizabeth Helms.

I just want to make a comment. I would certainly like to see a higher percentage, and I certainly think that we as patients need to be more accountable especially when we're going to enroll in a study; that we should be following through all the way to the end.

But one of the points I wanted to make is you can be also assured that if the patients that have these surgical procedures done were having problems, you'd be hearing about them. If their pain had increased, you'd be hearing from them because they don't pick up the phone, you know, when everything is good, but they sure do when everything is bad.

CHAIRMAN HEFFEZ: That's really not always the case in clinical practice unfortunately. Sometimes they don't want to hurt the doctor's feelings. Sometimes it's a financial reason. There's multiple reasons.

DR. BURTON: I guess having been involved with a number of studies and with both TMJ implants and TMJ surgery, I actually would agree with Dr. Heffez. I think it's almost the

opposite.

There are a lot of people who when they become dissatisfied go to someone else, and I will be honest. I've had a couple of people in the last month who had had other implants done at other points. I said, "Well, have you contacted your original surgeon and discussed this, you know, these burning issues with them?"

And the response is invariably candidly been, "No, I have not."

And these patients candidly were 18 to 24 months out, and they said, "Yeah, I was doing really well. I moved. I haven't gotten back."

Have you called and told them and discussed what's going on here?

And the answer has been no. So I get a little antsy personally when I say, "Well, they're just gone," and so they're going for geographic success. The truth is that an equal number of those may be geographic failures.

CHAIRMAN HEFFEZ: So I'd like to bring back the panel to this question. Okay? So I'm going to -- you see the question up there, and we've got three things here: pain intensity, interference with eating, and maximum incisal opening.

I am going to try to summarize what the panel said, and I'd like to hear if the panel is comfortable with what I've said.

The data that is presented does and we do feel it can be extrapolated for these points and we can expect that the outcomes will continue. However, it would be satisfactory to us if the company made an effort to obtain the additional data that it can do through mailings, and that we may see some variability in there, and that the company should, of course, continue to collect data.

But given this, these three points, that the data that's been presented does adequately reflect expected outcomes.

Would this be acceptable to the panel? I'm not trying to put words in anybody. I'm trying to summarize it so the gastric juices get satisfied.

(Laughter.)

DR. BURTON: Richard Burton.

I would say yes. I think given the parameters as you presented them, I would say yes.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

I concur with Dr. Burton and Dr. Heffez that, yes, it does.

DR. SUZUKI: Jon Suzuki.

I say yes.

CHAIRMAN HEFFEZ: Okay. Good. This is not a vote. We just sort of want to just get a general feeling.

I would like to jump to question four, and then we'll break for lunch. Okay? So let's go to question four.

The company plans to market the device that's noncemented or as a cemented fossa. In the clinical data set, some of the cases are with cement and some cases are without cement. Please discuss the data in light of these two different methods. Are there differences in outcomes?

So we previously discussed this issue, and that we did feel that we could consider the data of both the cemented and noncemented together, but I do think that I would like to ask the company. Mr. Pratt, is he in the room?

I'd like to ask Mr. Pratt: why does the company intend to market a cemented fossa when the two surgeons are not placing any cemented fossas anymore?

MR. PRATT: Joel Pratt with Lorenz Surgical.

The objective was to provide the surgeons as many

options, and if a surgeon felt that in a particular case cement was needed, they would feel comfortable doing so.

CHAIRMAN HEFFEZ: Well, we have now two experienced surgeons whoa re teaching this technique which we will talk about later as far as teaching modalities, but teaching the technique, and they're not teaching the placement of the cement.

MR. PRATT: That's correct.

CHAIRMAN HEFFEZ: I don't think I have to bring it any further.

Can you comment on that?

MR. PRATT: Dr. Quinn, would you tell us a surgeon not to use cement?

DR. QUINN: Peter Quinn.

I think this is more geared to the original application which used the term PMA cement or other media, and we were keeping in the possibility here, and I have strong hopes for this, that we will develop biologics and that sort of calcium phosphates with BMPs in them or something more biologic that ultimately might fit an application here.

That was some of the reasoning, but if that's not acceptable to the panel, my feeling is that we will continue to place these without cement.

CHAIRMAN HEFFEZ: So there are specifics to what you just said, and I think Dr. Runner should address that from the FDA point of view.

DR. RUNNER: I think the panel has to be reminded that we have to take the application on what is in the application. We cannot approve something on the possibility that something will be developed.

So either you will cement with what you cemented or you will not cement with what you have not cemented.

(Laughter.)

DR. QUINN: My opinion strongly is that this should be cementless. That is what we're teaching. That's what's working, and if we come up with another application, we'll have to do another study in the future.

CHAIRMAN HEFFEZ: Okay. Thank you, Dr. Quinn.

I would like Dr. Sinn to come to the podium and also give us your opinion regarding this.

DR. SINN: Well, my --

CHAIRMAN HEFFEZ: Identify yourself.

DR. SINN: Doug Sinn from Dallas.

My experience showed that early on in the first six or seven patients that I did that the cement really didn't add

anything to the case from my standpoint, and I actually was more happy once I took one pin off and just tested it, that I increased the stability much more by removing the pin than I did by adding the cement.

So I empirically discussed that with Peter, and we decided that we would try and make that change.

CHAIRMAN HEFFEZ: So you're both on the same platform.

DR. SINN: Absolutely.

CHAIRMAN HEFFEZ: Thank you.

Okay. Other questions from the panel? Dr. Patters, you had an earlier question or no?

DR. PATTERS: Mark Patters.

Dr. Heffez, you expressed my concerns far more eloquently than I probably could.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: My question then back to Dr. Quinn or to the individual from Lorenz.

Is the intent then or would you be more amenable to marketing it? Because obviously you removed the pin as of February this year. To market the device as an endless device without a luting medium, if you want to try to call it, whatever

you would. Would that be your intent to market it that way rather than sort of as an either/or?

MR. PRATT: Joel Pratt, Lorenz.

I think we would be very comfortable marketing only for noncemented use based on the two clinicians' experience.

CHAIRMAN HEFFEZ: Okay. So now let us just summarize.

Are there differences in outcomes? We feel that we can pool the data and that we're now talking only about a cementless fossa; is that correct?

Okay. Without any further comments, I think we can break for lunch and we would like to return precisely at two o'clock.

thank you.

(Whereupon, at 12:31 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:02 p.m.)

CHAIRMAN HEFFEZ: Okay. The second question that we need to address, I know we just finished lunch, but let's keep our attention to this. The second question is up there.

It's 132 of 180 cases were treated at site one, 40 of 180 cases at site two, and eight of 180 at site three and four and five. Does the fact that 96 percent, 172 of the 180 of the cases were treated only at two sites present a potential for bias in the clinical outcomes?

So I'd like to hear from the panel members. Dr. Patters.

DR. PATTERS: Mark Patters.

Of course it's potential for bias, but it works in both directions. It could bias the scientific nature of the project in a positive way and introduce far fewer variables. If there were ten sites and seven of the surgeons decided that in their hands they needed to put in two more screws than were in the protocol, then you'd be adding variable upon variable upon variable, and I think to be commended here are the two sites that only added one variable of taking the cement and cutting the post off.

But, yeah, in ten sites there could have been ten variables added, and the scientific validity of the study compromised. So of course, it's a bias, but it works in both directions.

DR. SUZUKI: Jon Suzuki.

I wanted to comment also I agree with Dr. Patters. I think that the variables have been at least minimized. There's always variables in any clinical trial, but the fact that the vast majority of them were conducted at two sites I think minimizes those outside factors and probably for the statisticians' sake it makes things a lot more streamlined.

And I also asked the question earlier today regarding a learning curve, and we were reassured that there would be a significant training period or training sessions for those surgeons that are going to be using thee particular products. So I don't think it's a problem.

CHAIRMAN HEFFEZ: Let me introduce a factor that I think that we should take into account, is that if there are only two centers to train people, is that feasible? That's something I think I'd like to hear how the other panel members feel.

Dr. Burton.

DR. BURTON: Richard Burton.

I think obviously that would be a significant thing, and the fact that you're not going to be on training might actually -- perhaps that should go back to Drs. Quinn and Sinn though. Do you have a feel I don't want to say what the demand is, but you know, are you going to be able to deal with the fact of being able to do that because, you know, again, what you were saying, Dr. Quinn, was that you were going to be or Dr. Sinn was going to be performing at least a surgery with these individuals when they started to utilize this system.

So, I mean, that's going to be sort of a rate limiting step, if you want to look at it that way, to any type of marketing attempt by the company.

CHAIRMAN HEFFEZ: I just wanted to touch upon that point, but it's going to be really addressed in question 6(b). So if we can just stay on track as far as whether it's presenting a potential for bias just in the clinical outcomes.

Dr. Li.

DR. LI: Steve Li.

I'd just pass along kind of a story from the VAS spinal cage panel that I was on in orthopedics. There was a multi-center; I think it was a ten or a dozen multi-centers, a

couple of dozen orthopedic surgeons involved in testing a spinal cage, and six of the two resident surgeons had a financial interest in the product, and the results from those six surgeons were about a 15 or 20 percent higher success rate than those that did not have a financial interest in the device.

Now, I don't think they were dishonest and the solution was not to give everybody a financial interest to improve the performance, but I think the message though is they had a level of expertise or knowledge about the device that was not passed on to the very next generation of surgeons. So that was probably a very close training situation where the first six trained the next two dozen, and yet there was still a very large difference in success rate.

Now, I don't know if that translates to this or not, but it certainly raises the issue that two centers done by two expert surgeons would probably reflect the best possible outcome.

CHAIRMAN HEFFEZ: Well, we certain can ask Dr. Quinn and Dr. Sinn if they can come to the podium and do they have a financial interest in the selling of the product.

DR. LI: Well, again, that wasn't my point, I think.

CHAIRMAN HEFFEZ: Yes.

DR. LI: Yes.

CHAIRMAN HEFFEZ: Go ahead.

DR. QUINN: I'd like to answer that question first. I have no patent in this. I have not received any stock. I have receive consulting fees over the past nine years, all of which have been donated to the University of Pennsylvania School of Medicine, Oral Surgery Giving Fund.

I have full intentions of being remunerated for time spent training other surgeons and putting courses on as a clinical service agreement, but actually with some great difficulty with the University of Pennsylvania Technology Transfer Center. We convinced them that it would be in the best interest to have Biomet maintain the patent on this device so that it's not held by me or the university.

To the issue of sites, Dr. Burton mentioned rate limiting. I'm somewhat in favor of rate limiting. I don't want the gate opened wide on this. I do think that we will broaden the site. In fact, the next proposed site is the University of Florida under Dr. Dolwick, who once he has training would become a trainer himself.

We try to identify sites based on both the expertise of the surgeon and the geography because I think that's important for the patients involved.

I don't have a specific gating of how this would go, but to extend this from two to four to six gradually would be my preference and not to open this up widely immediately.

CHAIRMAN HEFFEZ: Thank you.

Dr. Sinn, could you answer the other question?

Identify yourself just before.

DR. SINN: Doug Sinn from Dallas.

I, too, have no financial interest, no patent, or no relationship with Lorenzo other than as a consultant, and have received compensation for reimbursement for training or for traveling and that's all.

CHAIRMAN HEFFEZ: Thank you.

Any other questions from the panel?

(No response.)

CHAIRMAN HEFFEZ: So if we could summarize this question, do we all feel or it appears to me that we all feel that it doesn't really bias the clinical outcomes, and that in some ways it could be beneficial. Everybody more or less concur with that statement?

DR. PATTERS: I concur.

CHAIRMAN HEFFEZ: Okay. Very good.

We'll go to the next question. Fifty-two patients

of the 168 implanted patients had reports of adverse events. Of these 52 patients, eight required permanent devise removal. Please discuss the rate of adverse events in this patient population.

So if we look carefully at the adverse list, you'll see that actually the reporting was quite generous, reporting things that weren't really directly related to the prosthesis itself, but related to the surgical approach, for example, to it.

So I'd like you to look at that adverse list as a panel, and do you feel this list of adverse events is inappropriate?

Dr. Cochran.

DR. COCHRAN: This is David Cochran.

I think given the population that we're dealing with, this is a very low rate, in fact, and I'm very comfortable with it.

(Pause in proceedings.)

CHAIRMAN HEFFEZ: Excuse the silence for just one moment.

Dr. Runner?

DR. RUNNER: I saw Dr. Burton and Dr. Eggleston nod their head. Could they make those nodded comments more verbal, please?

DR. BURTON: Richard Burton.

I as one of the oral surgeon consultants to the panel and having been involved with TMJ surgery for, I guess, 20 years now, actually I feel that both the rate and the reporting -- I'd have to agree. Actually Dr. Cochran was reasonably liberal in their approach to that because, again, many things that were worded as adverse events were actually what most of us as surgeons -- and I'm not sure patients like that term -- but are part of the normal, accepted things that go along with just the surgical approaches to the joint or with any type of surgery whether it be infected, both the rates, the occurrence, and the resolution of those. We're certainly within the normal realms for this type of surgery, and in looking at the number of joints that had been lost within that time frame, with eight explanted joints out of that number, while certainly everybody wishes it was zero, it still is still historically looking probably a much lower number than most of us really would -- I candidly would have probably expected out of that population, even though the fact that this is not some ten or 15-year follow-up and in that amount of time, that is, again, both a reasonable number and a reasonable outcome.

CHAIRMAN HEFFEZ: Dr. Hewlett.

DR. HEWLETT: For me, in order to get a comfort level with this question, I tended to focus on the six reported cases

that were deemed by the investigators device related because of the generosity, if you will, in describing the other adverse events.

And even within those, there seemed to be some circumstances that, looking at it objectively, could perhaps even be not necessarily related to the device.

So given that, six cases, all but one of which appear to fall -- the adverse events occurred within that three-year period. I would tend to concur with the other sense of the panel so far that this is an acceptable level of adverse events.

CHAIRMAN HEFFEZ: Okay. Thank you.

Now, I'd like to tackle this issue which is related to two and three, and I'd rather tackle it now because we'll need to tackle it later.

Related to two and three I'd like to ask the panel regarding the indications because the indications are related to adverse events, and it's related to clinical outcomes.

We've discussed already previously that the indications are covered over approximately 11 rubrics, and the point has been made that the testing has been primarily in certain rubrics, and I'd like to know how the panel feels where the device has been properly tested, in which of those diagnostic categories.

So I enlist the panel members to look at the

indications and give me their comfort level.

During the silence I can help out and say at least there's osteoarthritis, and one of the points raised was the fact that many of these patients have multiple diagnoses and a primary diagnosis wasn't assigned.

But if you look at the numbers, you're looking at osteoarthritis, traumatic arthritis, total implant, avascular necrosis, ankylosis. Those are the big categories.

In a previous question, Dr. Quinn -- and I'll ask him to come to the podium just to confirm this -- did indicate that he felt that he agreed that the prosthesis had been tested better in certain cases, such as osteoarthritis and in other categories less well.

Do you want to respond to that?

DR. QUINN: Peter Quinn.

I would just like to make the point that I think in order to collect data we were trying to be very specific for the purpose of the study, to identify very specific diagnoses.

I think if you look at the two approved devices that are on the market, they both have the same indications, and I think there are five indications. They are much broader.

For example, one of the approved indications is loss

of vertical height of conduct. That would cover any of these indications. So I think in an attempt to collect more specific data, we may have painted ourselves into a statistical corner.

And I would suggest and maybe ask Dr. Runner if looking at indications of approved devices would actually be better guidance.

CHAIRMAN HEFFEZ: I'll ask Dr. Runner to help in the situation because we're not allowed to look at another -- you know, your PMA has to stand alone, but I'll ask Dr. Runner.

DR. RUNNER: I would suggest that the panel take into account this particular device and the indications that are listed on this device, and if you feel that there is not data, do you feel that you can extrapolate from the known condition to use of this device and whether that's appropriate or not?

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

One question I had. I just noticed this because of going back and forth, but in our panel packets there's a summary of safety with respect to this, and it lists ten indications for use, and then the essential prescribing information, which is very, very similar lists 11, and the difference is that it lists a number eight, and to make it 11, but number eight says degenerated or

reserved joints with severe anatomic discrepancies, which the indications for use in the summary sheet doesn't list that one.

So, I mean, I'm not sure. The first question is, and I guess it's probably back to you, Dr. Runner, is why there is a difference between the two, but I think that, you know, sometimes trying to make a difference between whether it's avascular necrosis, a degenerative rheumatoid patients, or a degenerated or severely resorbed joint really are in reality all the same thing.

So, I mean, I would actually -- I think Dr. Quinn may be correct here, in the fact that the specificity may not really be the issue. I think it's the degree of deformity, the degree of disability that the patient has is really probably the driving factor in making the decision to move toward some kind of a joint replacement as opposed to a more conservative procedure and whether it fits one of those specific categories may not be the best system of classifying it for that.

But can you answer why there's a difference between those two lists?

CHAIRMAN HEFFEZ:

DR. QUINN: I apologize for the discrepancy. I wasn't aware.

DR. RUNNER: This is Susan Runner. In terms of our review of the PMA, we looked at the indications for use list. The summary of safety and effectiveness is typically a document that's submitted by the company and is substantially revised at the end of the review process. So that really was not reviewed in detail.

The indications for use that was submitted with the PMA would be the primary indications that we went through for our review.

CHAIRMAN HEFFEZ: I have, Dr. Quinn, a question. If you look at the indications, in general they are all similar in the sense of lots of vertical dimension. One of them always that stands out is the development abnormality, and how many cases actually were treated with developmental abnormality to your knowledge?

DR. QUINN: I can't recall any that actually fell into that, offhand that fell into that category.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

It appears to me that Dr. Quinn has pointed out that there is no reason to believe that the device would behave differently in indications which were not studied, but I think

it's only appropriate that the sponsor indicate in the labeling that this use has not been studied, and there is no data. That would satisfy me.

There's no reason to think it would behave differently, but there is no data to say that it, indeed, does or does not.

CHAIRMAN HEFFEZ: How do the other panel members feel about Dr. Patters' statement?

You can sit down, Dr. Quinn. Thanks.

DR. BURTON: Richard Burton. I would agree with Dr. Patters on that. In our summary package, Table 2 was diagnosis, and it lists out 11 diagnoses some of which have been grouped within those surgical indications because the arthritides are grouped as one group, whereas they split out all three of the arthritides separately as part of their percentages, and it appears, at least looking at the diagnosis table, that there are listed indications in terms of surgical indications that thus far there have been no cases presented that fit that diagnoses.

But I think that what Dr. Patters and I would agree with is the fact that given the fact that these are all functionally equivalent in many respects, that you would not expect that this device or any other to perform any differently given the clinical

environment that they're in because clinically though the origin of the problem may be different. It probably would not affect the device itself once it was implanted.

CHAIRMAN HEFFEZ: So let me -- Dr. Runner?

DR. RUNNER: I just wanted to remind the panel that you can feel free to make recommendations about a more general indication for use or more specific as you see fit.

CHAIRMAN HEFFEZ: I'd like to maybe summarize the panel's position here and, please, I would like to hear from the panel how they feel.

We feel that the indications that the -- that the devices indicated for replacement of the temporomandibular joint and it has been well studied for perhaps loss of vertical dimension in osteoarthritic, traumatic arthritis, avascular necrosis, ankylosis, but additional studies need to be developed in order to study it in other diagnostic categories, to replace other diagnostic categories.

DR. RUNNER: Question. Are you stating that you feel additional studies need to be completed or you would prefer a labeling?

CHAIRMAN HEFFEZ: A labeling. I'm sorry.

DR. RUNNER: A labeling that would say that it has

not been studied in these conditions?

CHAIRMAN HEFFEZ: Dr. Runner, I agree, a labeling saying that the device has not been studied adequately for those other rubrics.

How would the panel feel regarding that? Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

I think having a caveat that in certain conditions there's been some data and in other conditions there isn't enough patients with that diagnoses had that labeling, I think it would suffice.

CHAIRMAN HEFFEZ: Okay. I've got a general consensus on that.

Now, there's one other point related to two and three that I want to cover, is that in some cases part of either the fossa, in most cases the fossa, but either the fossa or the condylar prosthesis was removed for reason X and that patient went through a certain period of time before receiving the other portion of the joint, prosthesis. In other words, they're walking around with a partial joint prosthesis. Is there a recommendation when that has to be replaced or is it adequate to let them function with a hemiprosthesis?

I'd ask Dr. Quinn or Dr. Sinn to address them.

DR. QUINN: We clearly don't believe in hemiarthroplasty as a general indication, but I think there are time periods that are determined by the cause for the initial removal. For example, in infection, and Dr. Sinn had a patient with MRSA that he can comment on, but we have reimplanted them up to two years later, and as short as three months later when the tissue condition improves to the point where it would be safe to reimplant it.

I'm not sure we could put a time period on it, but I think we could say there should not be permanent hemiarthroplasty indications.

CHAIRMAN HEFFEZ: So have you seen any adverse effects from waiting in a delayed fashion on those few cases prior to replacing the glenoid fossa, for example?

DR. QUINN: It was not a great n, but I think the biggest problem is deviation of the mandible to the side of implant removal. If there isn't gross deviation and, again, in multioperated patients where they're scarred, they tend not to deviate as much as somebody who has a de novo fractured condyle.

If there was gross deviation, and based on the deviation there was malocclusion and pain, I would tend to replace

it sooner than later, but we have replaced them up to two years later.

CHAIRMAN HEFFEZ: Thank you.

DR. QUINN: Can I ask Dr. Sinn to comment on his patients?

CHAIRMAN HEFFEZ: Dr. Sinn.

DR. SINN: Dr. Sinn.

The explants that I was involved in, one patient, as Peter mentioned, was a methicillin resistant Staph. infection, and that particular patient was a nurse in an emergency room and probably a MRSA carrier, and the explant was done both top and bottom on one side. The opposite side was left to function. It was not infected.

It was replaced three months later when we had tag white blood cell scans that were negative, and it got infected a second time and, in fact, explanted on the same side a second time., and it remains out to this day, and it's been about six or eight months since I took it out, and the patient is begging me to have it put back in because of the dysfunction that's associated with it.

But I've had no explants where I did partial removals. So all of mine have been complete. If I did, I did

three.

CHAIRMAN HEFFEZ: Okay. Thank you.

So I'd like to have a consensus from the panel that this device is -- as far as labeling is concerned, that we should consider not recommending it for partial joint replacement. How does everybody feel about that?

DR. PATTERS: Excuse me, Dr. Heffez. Mark Patters.

In the labeling that I see in all capital letters they say, "Do not use the individual components for partial joint reconstruction. So it's quite clear that they're insisting that it be used only as a total prosthesis.

CHAIRMAN HEFFEZ: All right. I'd like to move now on to question five.

The sponsor has provided engineering test data and a protocol for testing on both the new fossa design without a post and the fossa with a post removed using a rongeur. Do the engineering test data and protocol as presented given adequate safety and effectiveness information on the device?

Now, I understand that the information regarding the post being removed is to be forwarded to the FDA, but we haven't received that as of yet. If we presume that that information concurs with the data with the post -- I'd like to ask the question that

way -- is the data providing adequate safety and effectiveness?

I'd like to hear from Dr. Li.

DR. LI: Steve Li.

Actually I'm not sure the test is meaningful in either case. It seems to be unidirectional loading that doesn't really place the post anywhere in a biomechanically important function. So I think this particular test is not effective evaluating the device.

Secondary to that is as I said earlier I don't really think the presence of post, removing that post actually has serious or actually any biomechanical effect.

As long as I'm talking, can I raise things about testing or is this not the time to do that?

CHAIRMAN HEFFEZ: No, that would be a good time.

DR. LI: I guess I would rather see them test the things that I think are the big question marks in my mind. That would be obviously the wear issue, the polyethylene wear issue.

I'd like to test this concept of creep of the polyethylene around the screws that fits the polyethylene to the glenoid area. I just can't believe that those don't loosen in time. Maybe the amount of loosening is not clinically detrimental, but I would be very surprised if this happened at all.

And a third, much less important, I think we should at least check whether or not there's any chance of mixed metal crevice corrosion by using titanium screws against a cobalt chrome plate.

I think those three would be important features.

Also I think the screw pull-through test with the polyethylene also is not a clinically meaningful test. I think if you want to do that test, you might do it in conjunction with a pre-test. That would be the load to the flange, to the polyethylene flange and see if that actually causes creep because that's how it's going to pull through and loosen.

Once it gets to a loosened point, it's going to be loose. It will probably never really pull all of the way off the screws, but it could become loose to the point that it would be either poorly functional or nonfunctional.

So those would be my suggestions for additional testing.

CHAIRMAN HEFFEZ: While we're discussing this I'll ask Mr. Mulry or Dr. Mulry -- I apologize -- to circulate the device around the panel so that they can actually touch and feel it.

MR. SCHECHTER: This is Dan Schechter.

I don't know if anybody with the sponsor can answer

this question, but can anyone comment on how the testing done on this device compares to the similar devices, namely knee joint or hip point that has been mentioned a couple of times here today, how the testing compares at all specifically in terms of the specific tests that were done, pull through, et cetera.

MR. ROMAN: Shawn Roman.

Just to make sure I understand the question here, you want to know how the test results are --

MR. SCHECHTER: Not necessarily the test results, but the battery of tests needed in terms of a pull-through test, a T test. It was mentioned before that there was no or that you don't have a good fixture model to simulate TMJ motion. Are there fixtures like that for a knee joint that you use, just as an example?

DR. BERES: Ken Beres from Biomet.

I think in terms of the testing that was done, it's really a look at failure models, and we particularly ought to take fracture or failure modes.

And so you run it through the T tests and see does this flange break or does that break? And those tests are done, and these obviously and HIPS for a situation that mimics their use. Similarly, when we did a T test, we put it in a mock-up of a TMJ and you cycle it through ten cycles, which are really for

just breakage.

The idea of wear testing is a very good one, and we do that with hips and knees where there are simulators especially designed for those joints, to give you an answer. TMJ, I'm not aware of anything close to a simulator that could get us that data. It's a great idea, but I don't know of a machine that exists that would be capable of giving that data.

CHAIRMAN HEFFEZ: As far as the mechanical testing, I raised the point and asked if you had a comment on it before as far as many times you're testing all of this in vitro with the parts perfectly mated, but the value of testing it with them not perfectly mated, which would probably be a more realistic test. How do you feel about that? Would those tests be of value?

PARTICIPANT: I think that's an exceptionally important point. Even in the total hip joint where the contact stress and perfectly aligned, there may be only ten or 15 percent yield strength of the polyethylene. If you put the cut at a high induction angle and you look close to the rim, the contact stress gets up over the yield strength of the material.

So that the alignment and how the mandibular point would contact the fossa would greatly influence the contact stress and resulting failure mode of the polyethylene.

And just as a follow-up to Mr. Schechter's question, I think in general my general feel is that your in vitro testing should mimic what's going to happen in vivo. At least two or three of the cases of the test that provided by the applicant a reasonable materials test, but even they realized that they are not in vivo related tests.

So they're kind of a good material engineering thing, but they don't really help the patient, and so my suggestions are to try to point the testing and direction so that a result will give you some clinically meaningful predictive bound.

There's almost none of that as relates to the polyethylene.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: Susan Runner.

Correct me if I'm wrong. The company did set up their fatigue test model in a worst case scenario with the mandibular portion canted; is that correct?

PARTICIPANT: That's correct. As mentioned in my presentation, we incorporated three different conditions into the fatigue testing which were used to simulate worst case scenarios, one of those being angling the mandibular component at ten degrees with respect to the fossa.

DR. LI: Steve Li.

Wasn't that a worst case scenario for the mandibular component? Wasn't it still aligned on the fossa side?

PARTICIPANT: Well, the nature of the design is for the spherical head of the mandibular component to align with the spherical head and --

DR. LI: I understand, but my point is that the worst case scenario, the way I read their test description, the worst case referred to the mandibular side.

For instance, if you work perfectly -- I haven't handled the components, but I think Dr. Quinn said not perfectly performing. So there's a little bit of possible motion of the mandibular.

DR. QUINN: Actually the spherical head of the mandibular component has a smaller spherical radius than the --

DR. LI: Correct. So that gives the mandibular point of contact a range of places it could be, and some of those places are higher contact stress than others.

DR. QUINN: And that's why we had angled the --

DR. LI: But it wasn't clear to me that they were not mutually exclusive, but you could put you component at ten degrees and get contact with the fossa component at the exact same

place, or did you when you moved the mandibular component change the location of the contact point to the fossa?

DR. QUINN: I guess for the testing the center lines from the spherical radii that made the components work were aligned.

DR. LI: That's your interpretation. So it was the worst case for the mandibular side, but not necessarily for the fossa side.

DR. QUINN: Again, I don't see the difference there between them. You definitely would have a smaller surface contact between the mandibular component and the fossa component. So it would be a worst case scenario for the fossa component.

CHAIRMAN HEFFEZ: To come back to that, what did you test for? What are the tests?

DR. QUINN: All of the T tests were done with that angulation.

CHAIRMAN HEFFEZ: Thank you.

PARTICIPANT: As I understand, maybe just to clarify, it sounds to me like Dr. Li's concern, which I think would be well founded, is that the test occurred and produced some pressure and did not try to replicate any sort of either rotation or translational movement between the components.

DR. LI: That's correct.

PARTICIPANT: And I think that's the concern that's being raised.

DR. LI: And that -- I'm sorry. Steve Li -- that's exactly right, and also the location and the contact. In other words, as Dr. Rekow just handed me the components, if I could use my hands as the components, the mandibular component is here or it could be here, and the closer it gets to the edge, the higher the stresses get on the polyethylene.

So I would keep this contact area constant and change my mandibular component a long way, but yet if I don't move the location of contact, my contact stress on the polyethylene is the same.

So unless they specifically move the contact points as they move the mandibular component, they're putting the mandibular component in the worst case scenario, but not necessarily the polyethylene.

CHAIRMAN HEFFEZ: Yes.

MS. HELMS: Can I answer that?

CHAIRMAN HEFFEZ: Please identify yourself.

MS. HELMS: Elizabeth Helms.

I can answer that worst case scenario because this would be one of my questions and my key scenario. Ankylosis of

the right side, healthy joint on the left side. The ankylosis caused the left side to take the entire load, and the condyle went up into the fossa of the bone until it broke through the disc and then broke through the bone of, you know, the fossa.

I can't tell you the excruciating pain that's involved when you lose, you know, both sides like that, and so Dr. Li's question, I think, is really valuable because if you have a case scenario where you have one side that has a loss, what's going to happen to the condyle as it hits up into what is it, polypropylene? Is that right?

What will happen to that with that, and that's an intense load on the site, and you know, would it be fair to say that that kind of test has been done so that you would have a response because that is something that can happen in many cases.

CHAIRMAN HEFFEZ: Any further comments from the group?

DR. FAULK-EGGLESTON: This is Dr. Faulk.

We don't have a comment. We just had a question now that we've seen the device: why the indentation is on the top surface even on the site that doesn't have the little indented letter P or Y is there?

MR. ROMAN: All right. That is an undercut groove

of those included in the design to give an area for securing a bone filler or bone cement that does not extend above the top surface of the fossa component.

DR. FAULK-EGGLESTON: But now you're not putting in a bone filler.

MR. ROMAN: That's correct.

DR. BURTON: So Richard Burton.

So my question is, you know, it may not make a difference, but wouldn't you just have a smooth surface up there? It looks like it was an undercut obviously for retention, and you know, you eliminated the post offer here, but retained that.

MR. ROMAN: Yeah, I agree. Since we've discussed offering it as a cementless device, that undercut groove does seem unnecessary at this point.

CHAIRMAN HEFFEZ: However, these devices have been marketed and used and studied; is that correct, the cementless devices, since February?

MR. ROMAN: Yes.

CHAIRMAN HEFFEZ: Dr. Hewlett. I'm sorry.

DR. HEWLETT: I was just going to say or suggest that given Dr. Li's concern and the ensuing discussion that perhaps we've identified a potential condition for approval that might

be the appropriately discussed further during the voting.

CHAIRMAN HEFFEZ: Yes, but I think that if we could address this question right now specifically, I think we could say, if I can summarize what I'm hearing, that additional test data should be done in order to demonstrate adequate safety and effectiveness.

There were certain questions that were raised regarding where creep and mixed metals. Those were the -- now, how does the panel feel?

Dr. Runner?

DR. RUNNER: This is Susan Runner.

The question would be if the panel could discuss whether this testing needs to be done pre-market or post market.

CHAIRMAN HEFFEZ: All right. We could discuss that during the voting, but I guess we could ask: do the engineering test data and protocols presented give adequate safety and effectiveness information on the device as it stands?

How do people feel about that? Dr. Patters?

DR. PATTERS: Dr. Patters.

It appears so in my mind, and since they report no failures of the device in the 180 cases that it has been planted in, I feel pretty confident that the device is safe.

CHAIRMAN HEFFEZ: Dr. Bertrand?

DR. BERTRAND: Peter Bertrand.

Is that over a three-year period or longer, or are we restricted to a three-year period?

I know that Dr. Quinn's group and Dr. Sinn's group are continuing to collect data in three and four years. So we really don't know long-term effects yet, but over three years it does appear that it's fairly safe, but are we looking at it as far as making a judgment at three years?

DR. RUNNER: This is Susan Runner.

I think that for the purposes of this panel meeting we should look at it in terms of how the study was designed for three years.

CHAIRMAN HEFFEZ: So, Dr. Patters, you're --

DR. ANSETH: Dr. Anseth.

I just had a quick question for Dr. Li.

I think you had brought up some of your experience with the hip and knee implants, and based on the long history of using the ultra high molecular weight polyethylene and the cobalt chromium alloys, could you comment on if there were excessive wear, would they have seen anything, any other indications after three years of this study?

DR. LI: It's possible had they looked more carefully, for instance, with a more focused or more specific idea on the histological sections, perhaps closer view of the retrieved polyethylene components, perhaps even further analysis of the in vitro tests, had they made some more measurements on the laboratory test specimens. I think all of those were three potential sources of getting some idea of how much wear and damage is occurring.

But my concern is none of these measurements were made. So they may or may not be a problem. I guess that's my question or that's my concern.

DR. ANSETH: But in general, if wear becomes a problem is it seen later, so after? So would three years be on a very short time scale?

DR. LI: Three years would be on a very short time scale for something like osteolysis. You would have to have an enormous amount of wear, but we have unfortunately on the orthopedic side, I can think of three instances of devices that look great at three years, and there was a line for revisions at five because we just don't understand the wear rate. We just didn't see the wear rate at three.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: Dr. Li, I want to ask you another

question.

I agree that wear is a potential tremendously important concern. I don't know enough about the orthopedic literature to know if you get wear data and you can characterize the wear patterns and you can characterize the size of the particles, is the state of the science sufficiently well defined that we would know what those imputations are likely to be?

I have no trouble asking people to do more studies, but if we don't know what the outcomes of the studies are, I'm reluctant to impact their business for something we might not have anymore information other than some esoteric answers.

DR. LI: Steve Li.

An excellent question. I think all I can tell you quite honestly, in the laboratory, in vitro testing side is we've got tests that will tell you if you're going to be in really bad trouble. We don't really have a test to say if you're going to be okay. So therein lies the problem.

So at this point though, it's possible to be kind of in a not okay situation at two and three years and not really know it unless you actually go out of your way and look a little harder.

So I'm just worried that, in fact, it looks great.

In fact, the data looks great at three, but you run into things we've seen before that all of a sudden at four and five you've got a large revision business because of osteolysis.

Now, I'm not saying that's the case here. I just don't know.

DR. REKOW: As a follow-on question -- this is Dr. Rekow -- now I've forgotten the question. Are there any ways that you can effectively accelerate the test so that in vitro you could accomplish more cycles with heavier loads or something that gives you the same sort of things at least in the knees and hips in a shorter time span, that essentially gives you a worst case, but you could extrapolate a different time span than the three-year clinicals?

DR. LI: Those are really the descriptions of NIH grants actually.

To be fair to the sponsor, as far as I know, there is no, in fact, currently available TMJ simulator. However, the device has been around since the early '90s. In the early '90s there were no knee simulators either.

So for some reason this particular area has not devoted their attention to building one, but certainly there are no more degrees of freedom in a TMJ than there are in a knee.

So it is a possible thing to construct, but you might not have to go that far.

I mean, certainly looking with 180 devices out there, there might be enough clinical information from retrievals, histological sections, maybe pick a subset of groups to do a more close radiological study.

There are options where you can get a clinical sense for how much wear is going on. I guess I would like to see some measure of that, if not right away in the laboratory, at least some program to try to determine what level of wear they've got.

CHAIRMAN HEFFEZ: In the in vitro testing that was done, would you have expected to see where?

DR. LI: No, that's one of my concerns. I saw none of the in vitro tests that would actually, or at least the way they conducted the tests, that give me any indication of wear or creep results in there.

So it's possible had they done a similar work and made extra measurements they could have answered some of these, but the testing done so far, I think it's kind of an odd thing. The testing says the device is okay. The clinical results say at three years the device is okay. But I don't think they really had anything to do with each other

In other words, I don't think a laboratory test really dictated or predicted the clinical situation.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

I think one of the things we have to keep in mind though is the function on these particular joints. As was pointed out in the data, a lot of these patients have had five surgical procedures before this, and you've got 45 cases at three years with, as Dr. Patters pointed out, no indication of failure in any sort of way.

So although some of the in vitro testing would certainly be nice to see, I don't see that as a real necessity for us to go and make a decision in this case.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

I would agree with Dr. Cochran on that. I mean, I think that it's interesting. I can tell you that there's a bioengineering group at our institution who has looked actually for three or four years now trying to come up with a simulator with numerous attempts at things, none of which have been very successful.

I mean, I think it can be done, again, if you're

looking for grant money to try to do something like that, but again, trying to correlate what you might find in vitro with what we have at least found thus far in the clinical population doesn't appear that we're going to gain enough certainly at this juncture that would aid us making a decision either way.

I think, you know, we probably all hope that we will find some method where we can provide more adequate testing, and unfortunately at this juncture it doesn't exist, and I can't see how we can ask the sponsor to sit there and say, "Yeah, we ought to come up with a test, but we're not really exactly sure what it is and we're not really sure what we're going to find, and we're not sure what the correlation is going to be with what we find with the clinical presentation.

CHAIRMAN HEFFEZ: I will leave this question, but I want to just leave one statement, which is that the question is addressing the engineering test data. It's really not addressing engineering test data and its relationship to clinical data. It's specifically addressing the engineering test data.

So I just leave that, and then we'll come back to it when we look at conditions.

Six (a), draft labeling has been submitted by the sponsor and reviewed by the FDA. Please discuss the draft labeling

as presented.

Labeling is in -- everybody familiar where it's located? It's located in the back of -- the industry rep. and the patient rep. do not have this, but it's in -- for the panel members, it's located in the panel packet, one of the orange tabs. It's tab number three.

For industry rep. and patient rep., tab two.

The labeling from the sponsor describes a description of indications, contraindications, warnings, precautions, adverse events, clinical studies, how it's supplied, sterility, and it has a second section that describes patient information

So let's look at the first section, which is the actual prescribing information. I'd like to hear from the panel members.

DR. BURTON: Dr. Burton.

I have a question for Dr. Runner. You know, it made the comment in the question that these have been reviewed I would assume by your staff. You don't state much of an opinion, but the indications, like I said, are listed out being reasonably specific.

From a labeling standard perspective, would it be

better to perhaps maybe reduce the number and broaden them, including those particular areas, but I mean do we need to be or should we be this specific?

DR. RUNNER: This is Susan Runner.

I believe that the sponsor has developed the indications that it wishes to market the device as, and if you feel that there should be some changes, you should recommend it. But these are the indications that they started the study with, and these are the indications that they've presented to us to evaluate.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

I thought earlier we addressed that. We had data for some of the indications, and we were going to make the recommendation that for labeling that we don't have enough data on some of these other indications as part of the labeling process.

Did I misunderstand that?

CHAIRMAN HEFFEZ: That is correct.

DR. BERTRAND: So I think that applies to what we're looking at in 6(a) as far as indications.

DR. BURTON: Richard Burton.

Would we then, Dr. Heffez, would we then take that

existing list of 11 indications, look at the existing patients that meet those indications, and for those say that it is approved for those indications, and then for the ones for which there's insufficient data to show correlation, then sort of make them a subset?

I'm not sure. How would that be worded?

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I think at this point in time the panel could defer that to FDA for a more complete review after the panel meeting, if you so choose. I think it would be laborious to go over specific numbers at this point in time.

I do think that for this question though there was some discussion earlier about potential labeling for treating the patient for potential bruxes and more tooth contact, and that might be an addition that you might want to further discuss.

As I recall, Dr. Bertrand had mentioned that issue.

DR. BURTON: Dr. Burton.

I would agree with that, Dr. Bertrand, but in the contraindications, actually the last one, number nine, states that it is contraindicated in patients with severe hyperfunctional habits, e.g., clinching, grinding, et cetera.

So I'm not sure how we address it because they have

sort of already said that you really -- you know, their contraindications say that you really shouldn't put them in those patients to begin with.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: However, we've heard from Dr. Quinn that their patients had between 18 and 24 hours a day tooth contact. So that to me indicates some degree of bruxism.

DR. BURTON: Actually I think that regarding this item it should probably be moved up into the warnings as opposed to being in the paragraph. It should be listed numerically.

How do the panel members feel about that?

You have listed warnings, but I think one warning would be that emplacement of this device in patients with severe hyperfunctional habit, an undesirable outcome may occur, and I think that would be item number 617 in the one.

DR. RUNNER: I think there's some very specific literature about what's a warning, what's a contraindication, and we can --

CHAIRMAN HEFFEZ: Look at that.

DR. RUNNER: -- work at that.

CHAIRMAN HEFFEZ: Okay, but at least leaving this, we can suggest that we should look at where it's localized in the

document.

DR. RUNNER: Right.

CHAIRMAN HEFFEZ: The hyperfunctional habits.

DR. RUNNER: Right.

CHAIRMAN HEFFEZ: Yes?

DR. ANSETH: Kristi Anseth.

Also on the precautions, the number nine that talks about use of the system with filler material, and I thought that we had discussed this being a cementless system.

CHAIRMAN HEFFEZ: Correct. So that's something we should look at removing. Thank you.

I'd like to move to the second part of that, which would be the patient information, if we could look at that.

In the patient information, I notice the term glenoid fossa in one place and then fossa in another place. When it says what is a Walter Lorenz TMJ implant? It says, number two, fossa implant, and then when you go to what are the possible complications, it talks about glenoid fossa.

I think probably the patient might feel better with a diagram, for example, indicating what is the glenoid fossa and let them know it is a glenoid fossa. They may think it's two different terms.

Also, if you look at contraindications, you list active infection, but in the material for the physician, it says active or chronic infection, which is what are the contraindications for Walter Lorenz, patients with active infection, but contraindication for the physician is active or chronic infection. Just to be consistent.

I'll ask the company to consider maybe active foreign body reaction. I don't see that really listed there, but it is a concern with people with current prostheses undergoing foreign body reaction, that that should be treated before implanting a new device.

So I'm suggesting active infection, chronic infection, or foreign body, active foreign body reaction. I made those suggestions, but I'd like to hear from the panel how they feel.

Dr. Cochran.

DR. COCHRAN: It looks like the foreign body issue is addressed in number four and the possible complications under I believe that's the patient, under the patient information. It's not exactly what you said, but it at least addresses it.

CHAIRMAN HEFFEZ: That refers to the foreign body reaction to the material that they implanted.

DR. COCHRAN: Right.

CHAIRMAN HEFFEZ: But I'm referring to foreign body material on another implant that they're removing to put in.

Anybody else have any comments?

(No response.)

CHAIRMAN HEFFEZ: Okay. The foreign body reaction I think should be placed also in the physician information.

All right. We'll move on then to 6(b). Please discuss the need for training and the type of training protocol that may be necessary for safe and effective use of this device.

If I could just summarize what's been said up to now, that the principles involved feel that training at one or two sites and expanding those sites as people are properly trained is necessary.

I think that they have an audiovisual tape that has not been furnished to the FDA, and that they will have a protocol through probably continuing education programs that they will offer.

I'd like to hear from the panel how they feel in general regarding this. Also, perhaps we should think about is it possible, that it is very easy to do this early on in the course of a product. Sometimes as the product gets distributed it becomes

more and more difficult from the company's point of view, from a financial point of view from the company, financial view from the physician to do.

One minute. I see your hand.

I think that I'd like you to, panel and perhaps the sponsor, to consider that.

The other issue regarding training is a registry. Is the company -- will the company maintain a registry of all the devices that are implanted?

Dr. Runner.

DR. RUNNER: Susan Runner.

TMJ devices are tracked devices, and it's required to be tracked by the company.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: I think that I -- this is Diane Rekow -- I think that I heard that you were not going to make product available unless the clinician had been trained. Did I hear that properly?

Dr. Quinn is saying yes, and so I would like to make sure that that is explicitly included someplace because I really think that the points that we've made a number of times already today suggest the overwhelming need for careful, thoughtful

training and some hands-on experience probably before it just becomes available.

So that kind of requirement, I think, is an important one to include.

CHAIRMAN HEFFEZ: I think you have to take it one step further because with time everything gets diluted.

What is adequate training, you know? And are there only going to be approved sites, or can you go to someone who has already placed several and be trained by that individual even though it's not an approved site?

I think those things end up getting all muddled.

Dr. Runner.

DR. RUNNER: This is Susan Runner.

I think that if the training requirements are specific enough in the approval, I suppose approval order, any changes in that would have to come through a PMA supplement. So they would be required to maintain the training that's approved initially.

CHAIRMAN HEFFEZ: So the company should be careful in stipulating what should be the adequate training for this device.

DR. RUNNER: That's correct.

DR. BERTRAND: Question.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Based on the data we have right now, it almost seems like the labeling should say that there's only two places to be trained, the two major members of the study.

CHAIRMAN HEFFEZ: I think from a practical point of view you can't have the company coming here every time they want to add a site. So I think that they have to entertain how the training would be done so that it satisfies the panel, but at the same time doesn't box them into a corner.

Can I hear from maybe the President of Walter Lorenz? Mr. Pratt.

MR. PRATT: Joel Pratt.

This is really an important issue to us in that we want to certify surgeons before they're trained and train them and limit the distribution to doctors that are trained with this product.

However, in the long term, you know, if we look at three and four and five years down the road, Dr. Heffez makes a very good point of continuing the rigid training program three and five, as you said, may get diluted over the years and will depend on the ongoing results of the product.

I mean, I would envision that if we continued to train doctors and add doctors using the device and the clinical results are very good, we will continue to do that level of training. It's important for us to have obviously a very successful product clinically.

At the same time, and I guess I shouldn't address market issues, but -- well, I won't go there.

CHAIRMAN HEFFEZ: Actually, I think it's important if you could address them.

MR. PRATT: Well, there are two other companies that sell TMJ devices, and I don't know if they're regulated in how they train doctors.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I don't recall the specific label of either of the two devices. However, if you were going to require training for this device as one of the conditions of approval, again, if you're going to change that in any substantive way, you're going to have to come in with a supplement, which is not impossible, but you're going to have to justify why it should be changed.

CHAIRMAN HEFFEZ: Yes.

DR. FAULK-EGGLESTON: Yes, this is Dr. Faulk.

Yes, you need a lot of training, and I'm not

disagreeing with that, but if you make it so difficult that no one can get to the training, you've limited the product but you've also limited how you can help the patient.

So if somebody has okayed another device and you make it impossible for the individuals to get training, that's not fair to the patient either. So there has to be a medium between training and between availability.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

I would agree with Dr. Faulk on that. My question, although I've listened to this and I think probably harkening back to the days of dental implants when you couldn't buy them if you weren't blessed by the company and how that evolved, and I'm sure that that's sort of what Dr. Heffez is, is that over time as there is greater and broader understanding and use those things became diluted down.

And I think I certainly would agree with the sponsor in the fact that you have to avoid that because my memory -- and it's probably certainly no better than Dr. Runner's -- I'm not sure in the past that we ever recommended that or that there was ever any training contingency with that.

But I guess that, you know, your company and Dr.

Quinn and Dr. Sinn at least made comments on the fact that it was necessary or they felt it was necessary to have that. So you know, we need to reach some kind of an agreement here on what's an acceptable initial limitation that will be broad enough that will allow that to grow within the framework as we approve it at this point in time.

CHAIRMAN HEFFEZ: I think it's important, that we don't need to come to an agreement. We, the panel members, have to feel comfortable whether the device can be utilized or what level of training should be instituted to feel comfortable with this device being marketed. I think that's the question.

MS. HELMS: Elizabeth Helms.

Yes, I agree. I mean, the quality of the training is essential because if the quality isn't there, the patient is going to be put at risk again by somebody else, and we've seen this far too often happen to patients that have had or didn't get the quality of care because the education of the provider wasn't to the highest level or that they were rushed.

So the quality is very important. At the same time, how the patients access it. My question would be, you know, if there's only two sites that are training sites and a provider wants to come into the training site, does his patient come with him

there? And at whose cost is that going to be?

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I think that we're getting a little tied up in specifics of this training program. I think that the panel should recommend the level of training that you feel necessary, and the agency can negotiate with the company about the specifics of the training program.

CHAIRMAN HEFFEZ: So if I could summarize discussions that occurred previously -- thank you, Mr. Pratt.

MR. PRATT: May I make one more point? And that is that we do intend to expand the number of sites for training. Because of the burden that it would pose on Dr. Quinn and Dr. Sinn, we would like to have geographically around the United States and around the world centers where doctors can go and be trained prior.

So that would maybe address Dr. Faulk's question about access.

CHAIRMAN HEFFEZ: Thank you.

So if we could just summarize the comments made now and previously, I feel that I'm correct in saying that some training regarding this device is important, and that level of training, the specifics of it will be worked out between the FDA at another

time; is that correct?

DR. RUNNER: If that's what the panel feels comfortable with, unless they want to make more specific recommendations about the level of training.

CHAIRMAN HEFFEZ: I think we all -- and I'd like to have everybody say if they concur with me -- but they all feel that some level of training is required in order to put this device in.

There was multiple nodding for the tape recorder.

Yes.

MS. HELMS: Elizabeth Helms.

I'd like to say a high level of training.

CHAIRMAN HEFFEZ: Okay. With qualitative terms, it's extremely difficult to know what that means, but I think restated that we all feel that they require training regarding the actual surgical instrumentation and surgical technique.

DR. BERTRAND: Just one last comment. Peter Bertrand.

Dr. Dolwick, who is going to be the next person that you're going to train, thereafter with the degree of training of one or two surgeries, he then becomes eligible to train others, right?

Okay, and so is that the way it's going to be? Can we make that decision kind of right now? You have to be trained by someone already trained and that's the way it would expand in order to get centers at other areas?

CHAIRMAN HEFFEZ: I think those particulars we can let go for here and have the FDA detail with.

Ms. Scott was kind enough to tell me that if the panel feels that certain specific recommendations, such as you have made --

DR. BERTRAND: Well, I think that's a decision I was kind of asking the panel to say.

DR. RUNNER: Okay. We will take that under advisement.

CHAIRMAN HEFFEZ: So one recommendation would be that whatever test site the person doing the training should have at least been trained at least at one of these two sites or have had training on its own.

Yes, Dr. Li.

DR. LI: Steve Li.

Can I ask Dr. Quinn or Dr. Sinn? Are the biomechanical consequences part of your training? Like the biomechanical consequences of malalignment or off position or

having the joint too tight or too loose, is that part of the training, just out of curiosity?

DR. QUINN: Peter Quinn.

Maybe I could suggest some language that might be helpful, that we intend to do both hands on and didactic training. It should not be site specific though because I've gone elsewhere. It's more difficult with medical legal implications these days, but I've gone elsewhere. So I wouldn't want to limit it to sites.

But I do think if we use the term both "hands on" and "didactic" it would cover the high level that I think Ms. Helms is trying to get to.

To Dr. Li's question, yes, we intend to have a lab session where we can set up the prosthesis and best case/worst case scenario and discuss the biomechanical implications of the fit of the prosthesis.

CHAIRMAN HEFFEZ: Okay. Thank you.

I'd like to move on to 6(c). The sponsor intends to complete the pivotal PMA study following all patients for three years. Please discuss the need for any additional post market studies and issues that should be addressed were those studies to be required -- where those studies are to be required.

I'd like to hear from the panel. Any post market

studies that should be continued or should be instituted?

Dr. Li.

DR. LI: I'm agreeing that there might not be an appropriate in vitro test for wear, but I think as long as you have a metal on polyethylene, highly loaded joint, I don't think you could dismiss the possibility of osteolysis at a five-year or a six-year period.

So I'm not quite sure how we get our hands around following that up to make sure we just don't --

CHAIRMAN HEFFEZ: Well, we can --

DR. LI: I'm sorry.

CHAIRMAN HEFFEZ: Can't we request the company, I believe, Dr. Runner, to continue further than three years, to provide data up to five years? Is that correct or not?

DR. RUNNER: That is correct.

DR. LI: Also, while I have the microphone for a second, could I ask the sponsors who provide the example pieces, were those pieces tested or what was the source of those devices?

Can anybody tell me?

DR. RUNNER: Those devices were provided to F -- this is Susan Runner -- those devices were provided to FDA as examples of the devices.

DR. LI: Right, but were they tested before they got to you?

DR. RUNNER: I don't know.

DR. LI: Were these as new devices?

DR. RUNNER: I don't know the status of those devices.

MR. ROMAN: Shawn Roman.

To be honest with you, I'm not sure what the status of those devices were either.

DR. LI: Okay. The only reason I'm asking is the articular surfaces show signs of wear very much like a retrieved knee component.

MR. ROMAN: Okay.

DR. LI: And it's difficult to manufacture those surfaces with those particular features. So wherever those came from, they appear as if they were worn.

So whatever you did to get them, you did some sort of wear, and wear is occurring. So that's the only reason I ask. I'm sorry to get off the track.

CHAIRMAN HEFFEZ: I'd like to ask a corollary question. If the company has followed up to now 40 -- sorry. The number has escaped me -- 40-odd cases for three years; is that correct?

DR. RUNNER: Forty-five.

CHAIRMAN HEFFEZ: Forty-four. If that's all that would ever be followed up because of lack of follow-up, would that be adequate to the panel? Does the panel feel that would be adequate without any additional post market studies?

So just those cases because the statement is "follow all patients for three years." Assume no other patients get into that category. Would this information be adequate, that you would feel comfortable, that no additional post market studies would be issued or there were no outlying issues?

Dr. Runner.

DR. RUNNER: You're talking about the 180.

CHAIRMAN HEFFEZ: Yeah.

DR. RUNNER: All 180 would be followed to three years.

CHAIRMAN HEFFEZ: Right, but they didn't have any data to provide even for those 180.

Dr. Quinn.

DR. QUINN: A comment. Peter Quinn.

I believe pivotal PMA means the original 86.

DR. RUNNER: Well, we increased your study to 300-some odd entrances. If you have 180 patients enrolled at this time, we would expect them all to be followed through three years.

DR. QUINN: We expect to do that. I'm just questioning what "pivotal PMA" means.

DR. RUNNER: I meant the application as it stands now.

DR. QUINN: Okay, and at the risk of getting my statistical ears boxed by Dr. Janosky, we should realize that we closed the study March 31st. So there is further three-year follow-up already that's ongoing that can be provided because it is continuing.

CHAIRMAN HEFFEZ: So I'm not hearing anything from the panel. Dr. Rekow.

DR. REKOW: I'm comfortable if we ultimately could see the information that you're in the process of accumulating, but I wrestle with this whole wear issue, and I agree with Dr. Li that it needs to be done, and the paradox that I have is how to do it in a realistic and cost effective way.

And I'm really having a lot of trouble with that because that has been such a tremendous burden to the patients in terms of those systems that don't fail, and I personally suspect that your stuff is pretty good from what we've seen, but there's no data to assure that, and that's the real troublesome part.

And that's where I agree with Steve, and I don't

know that I can give you some really terrific guidance in terms of that, but it is an issue that I think needs to be addressed somehow.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Looking at your data, you have collected data on six years in some patients and five years and four years. Is that just something you're continuing to do naturally? Is it an intention to continue to do it regardless?

PARTICIPANT: Yes.

DR. BERTRAND: So you have beyond the confines of the study an intention to look beyond three years. That's great.

DR. FAULK-EGGLESTON: This is Dr. Faulk.

So what you're saying is it's no added burden or anything else to say that we would like to see the data through five years.

(Laughter.)

CHAIRMAN HEFFEZ: Dr. Quinn.

DR. QUINN: Peter Quinn. I'm sorry.

It's a tremendous burden, and I don't want to bring economics into this in a large part, but there is. This is a burden because this is all uncompensated care. If you understand how

insurance companies work, visits after 90 days are within the global period unless the gatekeeper or primary physician sees a reason why you have to go visit your doctor.

None of these are approved or reimbursed. So it is a burden that we have to take into consideration. It shouldn't drive this. We will continue to collect data.

I agree with collecting data on the original patient group. Whether we collect it at the same landmarks, I would continue to at least try to get yearly data after that, but it is a large burden.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: In regards to the wear issue, I do believe in some of our previous implant applications where this same issue has been raised, there was a condition of approval that indicated that retrieved implants should be further evaluated for wear, and that was one of the ways that we addressed that problem. So that could potentially be a condition that could be placed on this application.

CHAIRMAN HEFFEZ: From a practical point of view, Dr. Runner, who does that testing? Is it the company?

DR. RUNNER: The company does that testing.

CHAIRMAN HEFFEZ: Okay. I would like to close this

session and open up the public hearing. I'd like to ask if there's anybody from the audience who would like to comment.

This public hearing is being held before the panel actually has a discussion and votes.

Would you please identify yourself?

MS. COWLEY: I'm Terry Cowley.

The discussion of long-term follow-up I think is critical to the TMJ patient population, and our contention is that not only should you be following patients long after explanation because we've learned that the repercussions of implants seem to manifest throughout the life of the patient.

I understand the financial burden on the manufacturer, but it's an even greater financial and fiscal burden on the patient when the device fails.

Something which might be taken into consideration is that the NIH is going to hopefully fund through a contract an implant patient registry, and perhaps this is not the place to talk about it, but it would be one of the vehicles by which manufacturers would have the capability of having their devices assessed, the patient assured their device would be analyzed and their condition monitored.

So so much.

CHAIRMAN HEFFEZ: Thank you. Any other comments?

(No response.)

CHAIRMAN HEFFEZ: Okay. I'd like then to move to the next session, which would be open committee discussion and voting.

I'd like to proceed in this section in the following manner. There are three ways that we can vote for this PMA: approval, approval with conditions, and not approval.

I'm going to, based on the discussions that have been held, I would like to go around the table and see how people feel regarding these options. Based on the discussion, it looks like there would be approval with conditions. That's based on the discussion.

If I'm incorrect, please let me know, but I'd like to hear from each panel member how they feel.

To assist us in understanding what each definition means, Ms. Scott will assist us.

MS. SCOTT: If the panel will look in their packets, there is a document entitled "Panel Recommendation Options for Pre-market Approval Applications."

And I will read the options for the vote, and the definitions outlined in this document.

The medical devices amendment to the Food and Drug and Cosmetic Act required that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated metal device PMAs that are filed with the agency. The PMA must stand on its own merit as we have stated before, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of use outweigh any probable risk.

Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use will provide clinically significant results.

Your recommendation options for the vote as stated previously are as follows:

Approvable. Definition for approvable, there are no conditions attached.

The following agency action would be if the agency agrees with the panel recommendation, an approval letter will be sent to the applicant.

Your second option: approvable with conditions.

You may recommend that the PMA be found approvable subject to specific conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff.

Prior to voting, all of the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the conditions of your approval recommendation you want. For example, FDA follow-up or panel follow-up?

Panel follow-up is usually done through homework assignments to the primary reviewers of the application or to other specified members of the panel.

A formal decision of the application at a future panel meeting is not usually held.

If you recommend post approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: the purpose of the requirement, the number of subjects to be evaluated, and the reports that should be required to be submitted.

Agency action following this type of option. If FDA agrees with the panel recommendation and approvable with conditions letter will be sent.

Your next option, not approvable. Of the five

reasons that the act specifies for denial of approval, the following three reasons are applicable to panel deliberation.

(a) The data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling.

(b) Reasonable assurance has not been given that the device is effective under the conditions of use described, recommended or suggested in the labeling.

(c) Based on fair evaluation of all the material facts and your discussions you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

The agency action following this type of recommendation is as follows. If FDA agrees with the panel's not approvable recommendation, the agency will send a not approvable letter. This is not a final agency action on the PMA.

The applicant has the opportunity to amend the PMA to supply the requested information. The amended application will be reviewed by the panel at a future meeting unless the panel

requests otherwise.

Lastly, tabling. In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby creating ambiguity and delay in the progress of the application. Therefore, we discourage tabling of an application.

The panel should consider a not approvable or approvable with conditions recommendation that gives clearly described corrective steps.

If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

CHAIRMAN HEFFEZ: All right. So I'd like to hear from the panel how they feel. I summarized the discussions looking that we had some items that we needed to say and, therefore, approvable with conditions.

Am I correct in making that statement? So I see some nodding, and to make it easier, I will ask for a motion from the panel members that it be approved as approvable with conditions.

DR. HEWLETT: So moved.

CHAIRMAN HEFFEZ: Dr. Hewlett.

DR. HEWLETT: Dr. Hewlett.

So moved.

CHAIRMAN HEFFEZ: Second?

DR. SUZUKI: Second.

CHAIRMAN HEFFEZ: Seconded by Dr. Suzuki.

Okay. So in the future, whoever makes the motion, state your name first and whoever seconds it, state your name first.

Now, is there any further discussion on it?

(No response.)

CHAIRMAN HEFFEZ: Prior to the vote I will ask the opportunity for the FDA to make any comments before the vote. I will ask the sponsor if they have anything they want to say before the vote.

DR. PATTERS: Don't the conditions have to be decided before the vote?

CHAIRMAN HEFFEZ: Yes, that's true. I apologize.

Well, going around the table we all agree with conditions. Now we'll just go with each condition.

One condition, we'll try to -- so I will look for different conditions, but to keep it organized I'm going to suggest certain conditions, and if I leave any out, please let me know.

One of the conditions was regarding labeling. We felt that the labeling should be altered to reflect foreign body

reaction as a warning in both patient and physician information.

We mentioned severe hypermobility habits should be looked at as far as where its location is in the document and outlining it.

And we looked at the indications whereby we felt that some indications -- that there should be some statement saying that certain conditions had been well tested, but others adequate documentation is still acquired.

So I will ask you on this labeling issue for a motion. If I've left something out, please feel free to say, but I'd entertain a motion from the panel regarding the labeling condition.

Please, Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Was part of our labeling part of the clinician education also?

CHAIRMAN HEFFEZ: No. That's a separate issue.

DR. COCHRAN: David Cochran.

I'll make that as a motion.

CHAIRMAN HEFFEZ: So could you state the motion?

DR. COCHRAN: No way.

(Laughter.)

DR. COCHRAN: As you read them.

CHAIRMAN HEFFEZ: Okay. So I will restate the motion. The motion is that the labeling should be modified to reflect foreign body reaction in a warning in both physician and patient information; that the hypermobile patient or the hypermobile condition should be more clearly described and located appropriately in the document; and that the indications should reflect which of those indications have been adequately studied and in which indications require additional information

DR. REKOW: This is Diane Rekow.

And I'll second it, but I want to strike the discussion if I may.

CHAIRMAN HEFFEZ: Well, hold on just a second. I want to make sure that that motion is -- Dr. Cochran, if you agree with that motion.

DR. COCHRAN: Actually, all but the last part when you said about the indications requiring more data. I don't think we want to say requiring more data. I think we just say has not been evaluated.

CHAIRMAN HEFFEZ: Okay. So just to repeat the indication section, that the prosthesis has demonstrated efficacy in certain of these indications, but that it has not been demonstrated in the others. Fine.

So do you agree with that motion?

DR. COCHRAN: Yes.

CHAIRMAN HEFFEZ: Dr. Rekow, do you second that motion?

DR. REKOW: Absolutely. Second it.

CHAIRMAN HEFFEZ: Okay. Now, discussion. Dr. Rekow.

DR. REKOW: My discussion is taken care of. Thank you.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

By hypermobility, do you mean excess in function?

CHAIRMAN HEFFEZ: Yes. We can qualify the motion. Are you --

DR. BERTRAND: I would rather be more specific as to nonfunctional contacts in voting versus hypermobility.

CHAIRMAN HEFFEZ: So we're going to dismiss the motion. We're going to maintain a new motion. The new motion is that labeling should address foreign body reaction in the physician and patient information; that indications should indicate that -- that a phrase should be written to indicate that certain conditions have been -- that the efficacy and safety of the prosthesis have been demonstrated in certain conditions but

not in others; and hypermobile conditions reflects hyperfunctional habits, including hyperfunctional habits such as bruxes and clinching, should be addressed in a different location in the document.

Do you accept that motion?

DR. COCHRAN: Yes.

CHAIRMAN HEFFEZ: Dr. Rekow?

DR. REKOW: Yes.

DR. JANOSKY: Dr. Rekow seconds it.

Any further discussion?

(No response.)

CHAIRMAN HEFFEZ: The FDA, any comments?

(No response.)

CHAIRMAN HEFFEZ: And the sponsor, any comments?

(No response.)

CHAIRMAN HEFFEZ: So now we're ready for the vote. I'd like to go around the table, always starting from the same spot.

We are only voting on that particular condition. We're going to go through condition by condition, and then we're going to vote the whole thing after each condition. Okay? It will make it a lot easier.

So with this condition I'd like to go around the table. Industry rep. and patient rep. do not vote, and consumer rep. as well.

So Dr. Suzuki is the first one.

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Ed Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: Okay. Thank you.

So now we're going to go to condition number two. Again, just for simplicity's sake, I'm going to throw out a condition.

We discussed that physician education was of paramount importance. So I'm going to make a suggested motion and then we'll see how the panel feels. Okay?

I'm going to make the motion that one condition would be that all physicians placing these devices should be adequately trained according to -- no, that all physicians placing these devices should receive adequate surgical training prior to utilizing or implanting these devices.

DR. FAULK-EGGLESTON: This is Dr. Faulk.

Can you make that physicians and dentists.

CHAIRMAN HEFFEZ: Sure, although I understand the term "physician" at least refers to dentists.

DR. FAULK-EGGLESTON: Don't worry about it then. It's okay.

CHAIRMAN HEFFEZ: So I need someone to make a motion or they can obviously discuss the motion.

DR. COCHRAN: Could we have "didactic and hands-on training"?

CHAIRMAN HEFFEZ: Certainly. So the motion now reads that all surgeons who would be implanting these devices should receive adequate didactic and surgical or hands-on training for implanting the device.

DR. SUZUKI: This is Jon Suzuki.

I so move.

DR. BURTON: Richard Burton.

Second.

CHAIRMAN HEFFEZ: So I need any discussion. Dr. Patters?

DR. PATTERS: Yes. I'm Mark Patters.

Did you say "should" or "are required to"?

CHAIRMAN HEFFEZ: Are required. So let's repeat the motion. That all surgeons utilizing these devices are required to be trained didactically and hands on prior to utilizing the devices.

That's the motion. Dr. Suzuki?

DR. SUZUKI: Jon Suzuki, yes.

CHAIRMAN HEFFEZ: Dr. Burton, do you second?

DR. BURTON: Second. Richard Burton.

CHAIRMAN HEFFEZ: Any further discussion? Any further discussion?

(No response.)

CHAIRMAN HEFFEZ: I'd like to ask the FDA if they have anything to say regarding this motion?

DR. RUNNER: No.

CHAIRMAN HEFFEZ: No? And sponsor?

DR. BERES: Ken Beres.

I'm not a regulatory attorney nor a panel expert,

but maybe I could ask FDA. Is it the purview of the panel or FDA to regulate certification, accreditation, in that area?

I'm wondering if we're biting off more than we need to at this point.

DR. RUNNER: I'm going to defer to Dr. Schultz, our office director, deputy, soon to be office director.

DR. SCHULTZ: I'm going to address the question of should or required is a difference and has a legal term to it.

CHAIRMAN HEFFEZ: Let me try to --

DR. SCHULTZ: I'm sorry. My name is Dan Schultz. I'm Deputy Director of the Office of Device Evaluation.

This is something that comes up quite a bit in terms of the difference between accreditation and a requirement for the company to provide adequate training, and you're absolutely right. The issue of accreditation is something that the states and hospitals and other bodies are required to do, and that's their mandate. That's not our mandate.

But our mandate is to make sure that adequate training is provided when necessary for newly marketed medical devices. So I think that the wording needs to be somewhat to the effect which I think is pretty close to what I heard you say, and certainly we can modify it appropriately, but I think the idea

being that there needs to be a training program which includes both didactic and hands-on experience provided by the company for every user, every potential user of this device.

And I think we can work with the company to make sure that that is worded appropriately.

Does that answer your question?

Without talking about accreditation because I think that that's another issue.

CHAIRMAN HEFFEZ: So maybe let's redo the motion. Please, if you're going to address it, come to the podium.

DR. SCHULTZ: If I could answer that question, the training program will be required as a condition of approval. That's not "should." That is a requirement as a condition of approval that such training will be provided.

The issue of accreditation is another issue. So the training needs to be provided. As far as who does the accreditation, that's something that will be addressed elsewhere.

CHAIRMAN HEFFEZ: So I'd like to suggest another motion. The company must provide a hands-on and didactic training program for the surgeons who intend to use this device.

Dr. Suzuki, will you?

DR. SUZUKI: This is Jon Suzuki. I withdraw my first

motion and I make the second motion.

DR. BURTON: Richard Burton.

Second it.

CHAIRMAN HEFFEZ: Does the FDA have any other further comment?

(No response.)

CHAIRMAN HEFFEZ: And now the sponsor.

DR. QUINN: Dr. Quinn.

And I may have introduced the term and I apologize. I prefer if the use the term "clinical and didactic." We may have some credentialing medical legal issues in terms of how we allow physicians to enter other hospitals and actually touch patients in this current.

So clinical and didactic would mean that they would observe surgeries, participate in them to the degree, but "hands on" may be too far based on the different jurisdictions that we'd have to do it, but I think "clinical and didactic" would cover it.

CHAIRMAN HEFFEZ: Well, hands-on training does include laboratory work.

DR. QUINN: If that's understood, I agree.

CHAIRMAN HEFFEZ: Yes. So it does include laboratory

work. It's not patient hands on necessarily.

Do you want me to qualify that in the motion?

DR. QUINN: I think that would be helpful unless it's just understood that hands on could include both observational and laboratory.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: This is Dr. Runner.

I think that these are recommendations from the panel to FDA, and FDA will work out the specifics of how it will be worded in the approval order.

CHAIRMAN HEFFEZ: Thank you.

So we have no further discussion. Now if we can have a voting around the table starting with Dr. Suzuki.

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Edmond Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: Okay. We're now going to move to another condition. From our discussions, I'm going to suggest the following condition: that additional post market in vitro study be done to study the wear characteristics, the creep in relationship to the polyethylene, ultra molecular weight polyethylene, and the combination of metals, titanium, chrome, cobalt, and that these are post market studies.

There's sort of a motion that's waiting for a fish to catch.

DR. REKOW: This is Diane Rekow.

I'll propose the motion.

DR. LI: Steve Li.

Clarification. You suggested those as post market approval studies? Is that what --

CHAIRMAN HEFFEZ: That's what I'm suggesting. Just so the panel understands, certainly we could make it a pre-market study as well. I'm suggesting post market study. I'm trying to glean the information that we had. Some people felt comfortable with the clinical data having been -- you know, we have a certain amount of clinical data for three years.

That information would be helpful, and so that's why I suggested post market studies. Certainly the motion does not have to be seconded.

DR. RUNNER: This is Susan Runner.

You said in vitro, I believe.

CHAIRMAN HEFFEZ: Yes.

DR. RUNNER: I was wondering if the creep study would be in vitro and the wear and corrosion studies would be from explants. Is that correct or would the corrosion also be in vitro and that only the wear be from explants?

CHAIRMAN HEFFEZ: I'd like to actually if I can ask Dr. Li how he feels regarding those studies.

DR. LI: Well, I guess given the excellent clinical results for three years I would be comfortable making it a post market test. I guess if I could clarify, on the creep test I would be looking specifically essentially for the preservation of the fixation of the polyethylene with the screws. So I'm really looking for whether or not that fixation of the polyethylene to bone is going to maintain its original stability, if you will.

As far as the wear test goes, if it's post market, I would be in favor of developing some type of wear test, certainly after I've seen these that appear to have wear to them, both an

in vitro and an in vivo assessment of wear if it's going to be post market. I see no reason not to develop even some kind of evaluation for wear.

And I guess I would add in there actually as long as it's post market the effects of malposition or nonoptimal position of the components.

CHAIRMAN HEFFEZ: What Dr. Runner was trying to indicate -- do you feel those studies should be in vitro or in vivo?

DR. LI: Well, I think the wear needs to be both. Going down the line, I think all those things have to be evaluated on any retrievals that come out.

CHAIRMAN HEFFEZ: That's clear. How about in vitro?

DR. LI: Okay. In vitro I think you should do the wear test. I think you should do the stability of the fixation with time. I don't think the corrosion test is a big enough issue to develop a laboratory test for. I think analysis of retrievals would give you sufficient information for that.

CHAIRMAN HEFFEZ: Okay. Dr. Rekow, did you want to say something before Dr. Li spoke?

DR. REKOW: No. We're on the same page.

CHAIRMAN HEFFEZ: So let's look at the motion again.

That one condition would be that all explants would be retrieved and studied for wear, creep of the ultra molecular weight polyethylene, and possible corrosion, and in vitro testing to be performed to study wear and creep.

DR. LI: As far as the wear assessment, I'm including in that like a histological evaluation of collected tissue on retrieved implants as well as looking at the implants.

CHAIRMAN HEFFEZ: So the wear issue would involve microscopic and macroscopic debris.

DR. LI: Right, and an in vitro test includes nonoptimal positioning of the components.

CHAIRMAN HEFFEZ: So let's try another motion. The motion would be that all explants would be studied in regards to wear, microscopically and macroscopically, creep of the ultra molecular weight polyethylene, and possible corrosion at mixed metal sites.

In addition, that we're recommending in vitro testing in which there would be microscopic/macroscopic testing of wearing, including optimal mating and suboptimal mating of the devices, as well as a study of creep of the ultra molecular weight polyethylene.

That's the motion. How do people feel?

DR. LI: Steve Li.

So moved.

CHAIRMAN HEFFEZ: Looking for a second.

DR. BURTON: Richard Burton.

Second.

CHAIRMAN HEFFEZ: Okay. Any discussion?

MR. SCHECHTER: This is Dan Schechter.

I'm not sure how the panel feels, but with respect to the suggested test in vitro for creep, even Dr. Li indicated that an indication of some creep in screw holes may have no clinical significance. So I'd want to put the caveat to FDA in formulating an actual requirement that it be something that they could actually get meaningful data in vitro.

Given that there is no TMJ model existing in vitro, the fact that they may have some small creep could mean nothing. So I know I don't have a vote here, but I'm a little uncomfortable with that requirement.

The other comment, on the requirement for testing the bimetal junction, there may be existing test data from other products or other research done since these are common metals used in implants, and if that is done, perhaps that would satisfy the panel.

CHAIRMAN HEFFEZ: It's not common to combine those two metals.

MR. SCHECHTER: Okay.

CHAIRMAN HEFFEZ: But as far as the creep is concerned -- it's not. Did you wish to?

MR. MILLER: Dane Miller from Biomet.

And, in fact, it is common to combine those two metals.

CHAIRMAN HEFFEZ: You're referring to titanium and?

MR. MILLER: Titanium and cobalt chrome. In fact, they are probably used, by our best estimates, around the world 250,000 times per year, combination of hips and knees.

CHAIRMAN HEFFEZ: I stand corrected.

Is there data regarding corrosion on that?

MR. MILLER: There is a good bit of both in vivo and obviously or in vitro and obviously in vivo results that support the suitability of those two materials in combination.

CHAIRMAN HEFFEZ: What is the data regarding corrosion? Is there corrosion?

MR. MILLER: They are galvanically very similar and typically a combination of cobalt chrome femoral head and a titanium stem. There were early concerns, but those were not -- they did

not turn out to be an issue clinically, and that combination has been used, along with several other combinations of titanium and cobalt chrome, for something approaching 20 years.

CHAIRMAN HEFFEZ: And is that material used -- how long has it been used for the temporomandibular joint? Just curious.

MR. MILLER: I believe we were the first application of it there.

CHAIRMAN HEFFEZ: Okay. Thank you.

I stand corrected.

As far as the creep is concerned, Dr. Li, are we really looking at the creep for loosening of the device; is that correct? That's the important portion of it?

DR. LI: Correct. So I would be looking for some signs of loosening of the device. It could be actually in the existing test that we already give them that information if they would just assess it. So I'm not necessarily asking for development of a new test.

I just want some measure if it's going to be something I'm going to have to worry about or not, and I guess my question to Mr. Miller on the corrosion is: does the use of the screws, titanium screws in a titanium plate of this relatively thin

thickness compared to what's used in the hips and knees give you any concern?

In other words, a micro crack is something that's 20 millimeters thick. It is not the same as a micro crack in something that's a couple of millimeters thick. Do you have any sense for that?

MR. MILLER: This is Dane Miller again.

I hadn't intended for this to get into a long discussion about the characteristics of the surfaces and how they interact, but to answer your question, yes, certainly the thinner the surface, the smaller the component, the more concerning a crack is.

However, we apply the titanium plasma spray coating in a fashion that it's attached to, but not mechanically bonded completely to the substrate. Therefore, any notch sensitivity may occur because the characteristics of the titanium coating is not expected to propagate into the material itself, into the cobalt chrome substrate.

DR. LI: Steve Li.

I was more concerned about where the screw contacts the plate rather than the coating, where you have a titanium screw through the cobalt chrome plate.

Would you expect to see corrosion there and would you expect it to be a problem with the relatively thin titanium plate?

MR. MILLER: I wouldn't expect there to be any more a corrosion problem there than at the junction between a cobalt chrome head and a titanium femoral stem or the combination of plasma spray coating of titanium on a cobalt chrome substrate. I wouldn't expect there to be any differences, and in fact, titanium screws have been used in combination with cobalt chrome plates, especially in revision surgery where complicated revision has to take place.

DR. LI: Just one more. I don't mean to beat a dead horse in this relatively small issue, but, again, those are relatively thick components relative to the mandibular plate. So given that crevice corrosion occurs, for instance, on a femoral add against the titanium stem, that amount of corrosion is small relative to the size of the stem.

But if you have the same amount of corrosion in this particular case with a much thinner plate, would you expect there to be a problem where you don't have it with a large fracture fixation plate or a femoral neck?

MR. MILLER: This is all very subjective, but number one, I'm not aware in the case of a cobalt chrome femoral head

or any combination of cobalt chrome and titanium that it has led to crevice corrosion cracking that led to any gross failure of product, number one.

Number two, I would expect with smaller components that that amount of corrosion to be smaller, but we're talking in very qualitative terms right now. That could all be quantified with testing, but I wouldn't anticipate any greater a problem.

DR. LI: Thank you.

MR. MILLER: Thank you.

CHAIRMAN HEFFEZ: So this motion. Anybody like to vote on it? Dr. Suzuki?

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Ed Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: Okay. And from our previous discussions there appear to be one concern that some information could still be obtained from following patients to a mailing to complete VAS, visual analog scores or scales.

How does the panel feel regarding entertaining a motion that the company should try to complete as much of the missing data, even if it's only partial data, if the patients can't come for follow-up using mail-in instruments?

Dr. Cochran first.

DR. COCHRAN: David Cochran.

Can we incorporate into that the fact that we're going to follow the 180 patients up to three years as well?

CHAIRMAN HEFFEZ: Okay. Dr. Patters.

DR. PATTERS: I was going to suggest that, and I would suggest further that what we state is that they seek full or partial data on all 180 patients, 180 cases. I'm sorry. Full when available, and partial when full is not available.

DR. REKOW: Can I?

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: I just want to know how you feel about this. The study was approved for 300 patients. They've started 180. Do you want the whole study or do you want the 180 that have

already started to be completed?

DR. PATTERS: I think that that's all --

CHAIRMAN HEFFEZ: Dr. Patters?

DR. PATTERS: Well, I would ask FDA. The fact that it's approved for 300, that's a maximum. That's not a minimum, is it?

DR. RUNNER: That's correct, and we would expect at this point in time the 180 that have been enrolled to be followed for three years, and if additional patients are enrolled, for them to be followed for three years. Any patients enrolled in the study would need to be followed for the full three years.

DR. PATTERS: And that is what I suggest the motion be, but add to the fact that those patients who they are unable to get full data, that they should seek partial data.

DR. LI: Clarification.

CHAIRMAN HEFFEZ: Yes, Dr. Li.

DR. LI: Steve Li.

When you say follow the 180 cases for three years, does that mean some of them then will be followed up for five and six years? In other words, you don't stop following patients once they get to three years, right?

DR. RUNNER: Well, for the purposes of the study

in terms of following the study protocol, after each patient has reached the three-year point, they are no longer in the study. That's it.

Now, whether the surgeon elects to follow the patient in a different fashion, that's another issue, but for purposes of the study, they're done at three years.

DR. LI: Just to say something controversial, Steve Li again. If it's a money thing, I personally would rather see them pay the money to follow those 45 patients out to six years rather than another 140 for another three.

DR. RUNNER: I think to be realistic for FDA, we can't have an open ended study. We have to have some parameters on a study.

DR. LI: Could I say -- Steve Li -- could I say I would want to follow those 45 patients until they reach a five-year endpoint?

DR. RUNNER: If that's your recommendation, you can.

DR. LI: So that's a possible recommendation?

DR. RUNNER: That certainly is.

DR. COCHRAN: David Cochran.

Just as a clinical investigator, if you're going to change the way the study is done, you bring up a lot of IRB

issues, and you're going to have to go back to the IRB, and so I think we had better consider all the ramifications, not just financial, but also on the investigators for the study.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Yeah, Janine Janosky.

I would like to separate the two issues of one is following for effectiveness and one is following for safety, and I think what you're talking about, Dr. Li, is following for safety.

Within the following for effectiveness, there were three parameters that were set forth, and that study was to close at the end of three years. So I think it is reasonable for us to put forth one of the conditions that that study remain open until closure date when that last enrolled patient had reached three years.

Now, the issue of whether we want to follow them longer for safety, that's another issue, and I would suggest that we discuss that separately from completing that study for n equals 180.

CHAIRMAN HEFFEZ: Question to the FDA. Do you separate safety and effectiveness?

DR. RUNNER: Well, for purposes of the approval, you should be looking at both. However, if you feel that after

the three-year point you would like additional long-term data, then potentially a different type of study or an additional with fewer points or different types of endpoints could be entertained by the company.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky again.

I'm not suggesting that we separate safety and effectiveness for those first three years. I'm elongating this study in the arm of the safety arm also based on some panel members' comments that what actually happens, and I think Dr. Burton at some point says that you expected to see a lot of failures 18 months and out.

DR. BURTON: Well, speaking from experience, with most devices it was really in that two to three-year point. So I don't know if it was a honeymoon period or whatever else, but that it took wear components or something else because, again, certain other situations -- there was more wear debris, but it seemed to me in what I have looked at in the past it's at 24 to 36 month point is when you started to see those failures really start to occur.

And up until you got to about two years, it was sort of like, yeah, just about everything works at that point. And

whether it's cumulative effect, wear, debris, whatever factor you might want to focus in on, it seemed to be that period where you start to have those issues come forth or later, and that's what Dr. Li was saying, was the fact that maybe there are changes that are occurring at 36 months. Unfortunately we're not really capable to detect them, that might become more apparent at a four or five-year point.

I'm just personally, when I'm listening to this back-and-forth, I'm just a little uncomfortable, you know, having done investigatory work and having done work with -- I'm a little uncomfortable with we're still sort of changing horses here in the middle of everything, and I'm not sure exactly how or why we're going to be able to effectively do that and do it in a fair manner.

CHAIRMAN HEFFEZ: Okay. So let us do --

DR. JANOSKY: Can I just add one thing, please? This is Janine Janosky again.

For the long term safety issue, the registry might take care of that. AE event reporting might take care of that. I just want to separate the issue that was brought up by many panel members, is what is the long-term effect in terms of safety profile.

DR. REKOW: And if I could add one more thing.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: This is Diane Rekow.

If the sponsor is required to do analysis on the retrieved devices, we'll be able to glean some of that data at any rate.

CHAIRMAN HEFFEZ: Okay. So here's the motion. For safety and effectiveness, all 180 cases should be followed for three years to completion of the study, revealing all partial and full data. This should include retrieving visual analog scores from patients who or from long distance patients.

That's the motion. How does everybody feel?

DR. LI: Steve Li.

Could I ask a question, I guess, on the registry? What information is in the registry? Is it just like they're still on the patient; they're not on the patient?

DR. RUNNER: The registry doesn't exist at this point in time. That's a proposed grant that NIH is working on.

However, from FDA's purposes, all patients that receive these implants will be tracked. Therefore, the company will know where these patients are.

CHAIRMAN HEFFEZ: Could we stick to the motion that I am suggesting? I need somebody to --

DR. REKOW: I so move. Diane Rekow.

DR. SUZUKI: Jon Suzuki.

Second.

CHAIRMAN HEFFEZ: Okay. Any further discussion on it?

DR. LI: I'm sorry. Steve Li.

Can I add something and you can all vote it down if you don't want it?

CHAIRMAN HEFFEZ: Sure.

DR. LI: But I would like to follow at least those 45 patients or whatever the number is that are at three years to a five-year period in addition to finishing the 180.

CHAIRMAN HEFFEZ: Dr. Patters?

DR. PATTERS: Mark Patters.

I feel if Dr. Li would like that as a condition, that's a separate condition and he should raise that after this motion.

DR. LI: Okay. Fair enough.

CHAIRMAN HEFFEZ: Sponsor, did you have something you want to say?

MS. VERSTYNEN: Mary Verstynen.

I want to go back to the original study protocol

and the sample size calculation where we statistically justified a patient population of 86 years (sic) that we would follow out to three years, and that calculation was based on a delta of a one centimeter improvement in pain, which we have far surpassed.

And we were more than willing to follow the 86 patients. As the study advanced and Dr. Quinn and Dr. Sinn started enrolling more patients, we did an IDE supplement and bumped the population up to 200 to make sure that they could serve the needs of their patients.

We could have stopped it at 86 and this discussion would be going on of 180. The 180 is an arbitrary number based on when we submitted our PMA.

The next thing is that then we did an IDE supplement, and we asked for 300 because we were approaching the 200 mark. It seems reasonable to me that -- it seems like as a company and a study sponsor we are being penalized because we allowed this device to be implanted into more patients than what we originally anticipated.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: Despite the fact that you had 86 patients originally, you have enrolled 180 patients in this study. We would expect all 180 to be followed through.

MS. VERSTYNEN: And I guess the other thing, too, is -- and I agree with that -- I believe this is a device that requires post market surveillance. So it seems to me that what we should be discussing is what the post market surveillance requirements will be, not the completion of the IDE.

MS. SCOTT: May I interject at this point?

This is a recommendation by the panel. If the panel believes that the information presented is acceptable, they can make that determination. If the panel believes that there is additional information that should be added as a condition, they can make that determination based on their agreement or disagreement with how the study was designed and things of that sort.

FDA works with the sponsor in the IDE, but the panel can agree or disagree with what FDA has worked with the sponsor and what the sponsor has presented, and it is a recommendation to the FDA, and then following that, the FDA and the sponsor can work together.

But at this point, it's the panel's recommendation to FDA as what they believe is appropriate to approve the device at this point. The motion is approvable with conditions.

DR. FAULK-EGGLESTON: Jan Faulk.

The other issue is you went from one device that was cemented, and then now you have a device that you don't use the cement, which needs, I would suspect, different follow-up. So you can't just drop with the cemented items and then not get data on the ones that aren't cemented.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

Like I said, I guess I'm sympathetic with what the company is saying, but in my opinion, when you requested and expanded that, the IDE refers to 200 and then I guess eventually into three. Certainly you don't have to enroll further patients at this time and continue it to 300 patients, but when you accept this responsibility and the ability to continue the study to that 180, it seems to me that you would accept to some degree the decision then to follow at least that group out to the three-year study point as you would have any of the other patients.

And I guess I'm a little uncomfortable with then suddenly deciding, well, we're going to go to that 86 on out, but the other, you know, 94 patients at this juncture we'll sort of disenroll them and abandon what data that may represent, which again, as Dr. Faulk pointed out, includes a large number or the bulk of the number which had the noncemented fossa as well.

So I think to walk away from that also would limit the potential ability to evaluate the product.

CHAIRMAN HEFFEZ: There's a motion on the floor, and it's been seconded. Any other discussion?

(No response.)

CHAIRMAN HEFFEZ: So let us go. Dr. Suzuki.

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Ed Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: There's another condition that probably should be labeled as Label 2 condition, but the condition would be that we would remove all reference to cementing the prosthesis and the item should be marketed only as a cementless prosthesis.

Any comments on that?

DR. PATTERS: So moved.

CHAIRMAN HEFFEZ: So Dr. Patters made the motion. Anybody second it?

DR. FAULK-EGGLESTON: Jan Faulk.

I second.

CHAIRMAN HEFFEZ: Any discussion?

(No response.)

CHAIRMAN HEFFEZ: Okay. Let's vote on it. Dr. Suzuki.

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Ed Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: I'm sorry.

CHAIRMAN HEFFEZ: We're voting where we're moving cementless prosthesis.

DR. BURTON: I'd like to hear the motion again, please. I'm sorry.

CHAIRMAN HEFFEZ: The motion is that we would be

removing any reference to marking the item as a cement --

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: Okay.

DR. RUNNER: Could I ask a question, please?

CHAIRMAN HEFFEZ: Yes.

DR. RUNNER: Just for clarification, the fourth motion was to continue to follow all 180 patients to three years with full or partial data post market.

CHAIRMAN HEFFEZ: Yes.

Another condition was the FDA has yet to receive the report regarding the mechanical testing of the device without the post. So it is conditioned that the data regarding mechanical testing and engineering testing on this device without the post be provided to the FDA and does not demonstrate substantial difference between the engineering data on the device with the post.

Any comments? Anybody wish to make that motion?

DR. REKOW: Diane Rekow.

I so move.

CHAIRMAN HEFFEZ: Second?

DR. SUZUKI: Jon Suzuki.

Second.

CHAIRMAN HEFFEZ: Any discussion?

(No response.)

CHAIRMAN HEFFEZ: I guess we can go for voting. Dr. Suzuki.

DR. SUZUKI: Jon Suzuki, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. HEWLETT: Edmond Hewlett, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. FAULK-EGGLESTON: Jane Faulk, yes.

DR. BURTON: Richard Burton, yes.

DR. REKOW: Diane Rekow, yes.

DR. PATTERS: Mark Patters, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. COCHRAN: David Cochran, yes.

DR. LI: Steve Li, yes.

CHAIRMAN HEFFEZ: Okay. Now, Dr. Li, you raised a question about safety, want to follow patients up to five years.

Would you like to make a motion?

DR. LI: No, I withdraw that motion.

CHAIRMAN HEFFEZ: Are there any other conditions that the panel feels should be discussed?

DR. BURTON: Richard Burton.

Dr. Heffez, they had earlier made a comment about whether the panel makes any recommendations regarding the post market surveillance. Dr. Runner, do you feel there's any need for any recommendations from the panel regarding post market surveillance items?

DR. RUNNER: I feel that the recommendations that you've already made are post market surveillance items. If you feel there's some additional things that you would like the company to do, they should be added at this point because all of these are things that we will get from the sponsor, particularly the clinical data on the 180 patients up to three years.

DR. BURTON: Let me ask a question then. You know, you made reference to the fact that this item really just tracks the patients. There does not exist a patient registry, and what obviously Dr. Li was alluding to or at least my interpretation was that the fact is that what occurs in that three to five-year point, is there any place that that data would ever come back to

as we currently stand?

DR. RUNNER: Well, the adverse event data on patients post any marketing of any device should come to us through MDR and MedWatch reports, tracked items, as well as other devices that are on the market.

So it's incumbent on the surgeon and/or the patient to report adverse events to the agency post market, and there's methods in place for that to happen.

CHAIRMAN HEFFEZ: This appears to conclude all of the conditions unless another panel member has a condition that they would like to raise.

(No response.)

CHAIRMAN HEFFEZ: Not hearing any, I'm going to now entertain a motion that we approve this as approvable with conditions, and the conditions that have all been -- each of us have heard. If we want, we want repeat those or I think -- no.

So then we can go ahead and vote on approval with each of the conditions that have been outlined.

DR. BURTON: Would you need a motion?

Richard Burton.

CHAIRMAN HEFFEZ: We can discuss this. Yeah, go ahead.

DR. BURTON: I go ahead and move then. I guess I move the question because I think we had actually made that recommendation before.

CHAIRMAN HEFFEZ: Yeah, and you can second it if Dr. --

DR. BURTON: Okay. Richard Burton.

Second.

CHAIRMAN HEFFEZ: And for the record, who moved? Who made that motion? I need somebody to make that motion.

DR. HEWLETT: I believe I did.

CHAIRMAN HEFFEZ: I think Dr. --

DR. HEWLETT: Ed Hewlett.

CHAIRMAN HEFFEZ: Okay. Now, any further discussion?

(No response.)

CHAIRMAN HEFFEZ: So could we vote, just to change the pattern?

(Laughter.)

CHAIRMAN HEFFEZ: Before we vote, Ms. Scott was kind enough to indicate to me if the consumer representative, industry representative want to make some comments prior to this final vote.

MR. SCHECHTER: Dan Schechter.

Nothing at this time.

CHAIRMAN HEFFEZ: Sponsor has anything?

(No response.)

CHAIRMAN HEFFEZ: Okay. So then let's proceed to the vote.

Dr. Li.

DR. LI: Steve Li, yes.

DR. COCHRAN: David Cochran, yes.

DR. ANSETH: Kristi Anseth, yes.

DR. PATTERS: Mark Patters, yes.

DR. REKOW: Diane Rekow, yes.

DR. BURTON: Richard Burton, yes.

DR. FAULK-EGGLESTON: Jan Faulk, yes.

DR. BERTRAND: Peter Bertrand, yes.

DR. HEWLETT: Edmond Hewlett, yes.

DR. JANOSKY: Janine Janosky, yes.

DR. SUZUKI: Jon Suzuki, yes.

CHAIRMAN HEFFEZ: Okay. So that's a unanimous vote.

So I'd like to go from each panel member who voted and have a specific reason why you voted the way you did on record. So Dr. Li.

DR. LI: Steve Li.

I think the clinical record that you've reported

is excellent as far as you've reported it. My only concerns are those things that were essentially not tested, for which we don't have a clear assessment, but then time will tell if those things and if the post market approval tests are conducted.

DR. COCHRAN: David Cochran.

I felt that the material that was presented to the panel members, as well as the discussion during the day, fit the requirements as defined for both safety and effectiveness as defined for both safety and effectiveness for the device.

DR. ANSETH: Kristi Anseth.

I also thought that the results show and demonstrated safety and effectiveness and the conditions associated with the approval fill in some of the extra information about follow-up and labeling and some of the wear tests that weren't conducted.

DR. PATTERS: Mark Patters.

I believe the sponsor and their clinicians should be commended for the high scientific quality of the study and introducing minimal variables, and I feel that they've shown safety and efficacy.

However, I feel that conditions that require that they follow the subjects through three years as originally agreed is appropriate.

DR. REKOW: This is Diane Rekow.

I don't have anything to add, but I wanted to say the same things that Mark has just said because I really compliment you on the quality of the study, and I can't wait to see the papers that are coming out.

DR. BURTON: Richard Burton.

As an individual that's dealt a number of years with this patient population, which is a difficult population to deal with, and not the individuals personally, but their disabilities and the problems that grow forth from that, like was said, it's a very well done study, and I was certainly convinced by the data that was presented and the presentations that it is a safe and efficacious product.

And I think that, you know, the only questions that really I saw running around the table was looking at the long-term issues because most of us who have been in this particular arena for any length of time realize that sometimes the amount of time you have to study these kinds of issues, sometimes they don't come up to us within that time frame.

And I guess it's incumbent upon not only just the company but the surgeons that are utilizing it, and that's sort of, I guess, what I'm speaking actually to Dr. Quinn and to Dr.

Sinn, and that as you educate these people that they understand to be vigilant for those long-term issues as well.

Thank you.

DR. FAULK-EGGLESTON: This is Jan Faulk.

And my opinion is one as a clinician. You need increased modalities to help these patients. They are out there. They need help, and you need to do it in a better, more efficacious way than we've done previously.

DR. BERTRAND: I'm Peter Bertrand.

I voted yes for approval because I thought the data was tremendously well presented. I believe the company is following up and Dr. Quinn and Dr. Sinn are following up with an incredible patient compliance rate.

I also want to applaud them on their perceived need to sustain education long term both for clinicians and for patients.

DR. HEWLETT: This is Ed Hewlett.

I'm pleased to see that such a well conducted study is going to benefit a population of Americans who suffer from a malady with particularly high morbidity, as well as complexity and difficulty in treatment. So congratulations on that.

And I'd like to concur with the rest of the panel members that I'm quite satisfied within the limits of the additional

information that would be collected as a result of the conditions that safety and efficacy standards have been met.

DR. JANOSKY: Janine Janosky.

I view the ratio for effectiveness and safety to be a positive one for the intermediate data points, and I think the conditions that we applied to the motion will let us see whether that holds true for the final data point.

DR. SUZUKI: Jon Suzuki.

I voted yes because I feel the clinicians are outstanding; the protocol is scientifically sound; and the results are very satisfactory.

CHAIRMAN HEFFEZ: At this time I would like to thank all of the panel members, all of the consultants, patient representative, consumer representative, industry representative, certainly the FDA for all of the background work and effort.

And I certainly want to thank the sponsor for having the people here to answer all of the questions and all of their hard work.

At this time, this concludes this meeting, and again, I appreciate all of your efforts.

Dr. Runner?

DR. RUNNER: Excuse me. Before we go to the closed

session, I think Ms. Scott wanted me to present some plaques of appreciation to two panel members who are serving today as consultants, but who have officially gone off as permanent panel members.

And I have a letter and plaque for Dr. Mark Patters, who has been on our panel for a number of years, and this is a certificate of appreciation and recognition of your service.

(Applause.)

DR. RUNNER: A similar plaque of appreciation to Dr. Janine Janosky who has been stolen away by other panels for her excellence.

(Applause.)

CHAIRMAN HEFFEZ: So thank you very much for everybody, and I will ask everybody to clear the room when the FDA enters a closed panel, closed session.

(Whereupon, at 4:25 p.m., the meeting in the above-entitled matter was concluded.)