can evaluate that variable given over a million subjects, anything will achieve statistical significance. And as Dr. Goodman said, you may do that and have absolutely no clinical advantage in identifying a difference between individuals in the study.

So I would simply put that out as a plea that we use the terminology rigorously.

Thanks.

CHAIR KIRKPATRICK: Thank you.

I'd like to now revisit Dr. Pfeffer. Do you have any additional question or comment?

DR. PFEFFER: Yes, just a comment on Dr. Goodman's encouragement about the Buechel-Pappas and the range of motion issues. I think it is very important. It doesn't seem fair to eliminate the range of motion from a parameter and, therefore, bias against this study.

But if you do do that, and, as Dr. Goodman suggested, you do emphasize that, I'd

very much like to hear a commentary from you all about the subtalar range of motion issues which you know were important in this study and somehow, at the best, overlooked.

On pages 92, 58, and 78 of this book, there are comments about converting the total ankle to an arthrodesis. The question I have to all of you is is it really as simple as it sounds? I worry that these comments minimize that.

In other words, reading on page 92, beyond the clear benefits provided by the STAR ankle, there is little clinical down side to surgical treatment. This means that the present standard of care of arthrodesis is always an option for STAR ankle patients. So it is like well, if the STAR ankle fails, just go ahead and fuse it. And nothing is lost.

There is no good data on this other than what you own. But I think it is not so simple perhaps as just taking out the ankle. You've got a small amount of bone but there

may be great loss in taking out this tibial component, for example, which has now grown in.

So is it really true that you just simply convert these? And subtalar motion is not affected? Because my concern is if you operate on someone with normal subtalar motion and put a total ankle in place, and the ankle fails and you take it out, and you have to fuse with a femoral allograft, and you lose subtalar motion because of prolonged immobilization and bone loss, then you end up with a person who is worse.

So it is a small point but it is sort of glibly treated in this text. So that is one question that you could help us with now or later.

CHAIR KIRKPATRICK: If you have a brief answer to that, you are welcome to comment. I would recognize that he indicated it is a small point.

DR. COUGHLIN: Then I'll give a

small answer. I think that the point is well taken. And the literature shows that revisions after ankle arthroplasty has high rates of success. Kitaoka showed a 78 percent fusion rate after his series. Anderson, in Europe, published in 1998, showed a success rate of 17 of 21.

Now I'm not saying it is easy to fuse after an Agility ankle where there is a large component of bone that is removed. But that, indeed, is one of the strong points of this arthroplasty that we are removing a relatively small amount of bone compared to other arthroplasties which gives us an option that we can have a successful arthrodesis, as we did in several cases, and we can protect subtalar which, I agree with you, is of paramount importance.

DR. PFEFFER: Good. Thank you.

Just a few other brief questions, very brief. And it really has to do more with your future plans here.

One, if you could specifically tell us in your post-approval study what the role of the x-ray will be, Dr. Saltzman, in all his pivotal studies on the Agility ankle, taught the orthopedic community the essential role of radiographs, not just for evaluating the ankle lucency but also for range of motion.

I read somewhere that the x-rays in the post-study would be done when clinically appropriate. I'd like a comment on that at some point please. Will it be done on every single patient? And will dorsiflexion/ plantar flexion x-rays be done?

Should I ask the other brief questions I have?

CHAIR KIRKPATRICK: If they have a quick answer to that, they are welcome to. If you would rather wait until after lunch, just signify that to us. After lunch? Okay.

DR. PFEFFER: Yes. Also in regard to future plans, you have added a contraindication of adult onset diabetes

mellitus with no particular mention of why. I'd like to know why that is.

Also in your contraindications, since we know from the data, at least as I read it, that the continued access patients did better than the pivotal patients. And perhaps the deformity that the 12 percent versus 48 percent has something to do with it, will you modify your current indications for this ankle for someone with less than 35 degrees of deformity?

I think all of our concerns -- everyone, on both sides of this table, is that this ankle will be given to society and used inappropriately. So what guidelines do you plan regarding deformity?

Another just quick comment but the statistician can judge this more, back to the osteoporosis, small point but you eliminated some patients arbitrarily because of weight. You said two patients were almost 250, even though they were 260, so you said let's throw

them in. You said one patient was 283 degrees. And that was just too fat so we're going to keep them out.

You eliminated the osteoporosis patient mysteriously. I would suggest statistically that perhaps all of those patients should be put back into the study if it effects the data. And, again, that is certainly not my area of expertise.

CHAIR KIRKPATRICK: Excuse me, before you move on to the next question --

DR. PFEFFER: Yes, sir.

CHAIR KIRKPATRICK: -- I think Dr. Mann looked like he was ready to answer the deformity question. Or would you prefer to wait until after lunch?

DR. MANN: Well, as we pointed out earlier, the surgeons involved had a learning curve as well. And the degree of deformity was one of the things we learned about.

We analyzed their initial cases very carefully and we became less bold as we

became smarter. So I would say that the degree of deformity that we look at now, much more than ten degrees of varus and valgus probably is not -- would probably be a contraindication or a relative contraindication to the procedure.

But the main thing we need to look for is a plantargrade foot. Without a plantargrade foot, all bets are off as far as trying to put in a total ankle replacement. And that is another thing we need to consider.

As far as the diabetes is concerned, this opens up sort of a whole can of worms because the problem that you get into is these people sometimes will go out and develop a neuropathy.

And with a neuropathy come Charcot changes in the joints. And what is going to happen with your ankle replacement as the bone possibly weakens and collapses with the components in place? So that is one of the reasons we don't like to do that.

DR. PFEFFER: Good. This is really in with Dr. Skinner's area of expertise more but very specifically, from the best of limited understanding on this, you did a finite element analysis on the failure of the polyethylene component which was reasonable because certainly the 163 pound stress over ten million cycles represents normal walking at four times body weight.

Everyone would probably agree that up to eight times body weight, if not more, on heel strike that is forcible that can be transmitted across the polyethylene component. Is there a role for a test to failure? Or a static load test to failure that might have to be performed on these patients by a mechanically --

DR. SALTZMAN: I'm going to try to be fairly brief here. We had four fractures in about 600-something patients. The average weight was 89 kilograms. Two of them were in trauma, major trauma. One was put in a

patient with 35 degrees deformity. All of them had deformity and some ligamentous instability.

It is very hard to build a testing device, I think, to cover that. And Dr. Skinner is right. We didn't test varus and valgus. It is hard to test varus and valgus. I tested in our lab and we published in the British Journal varus and valgus and what happens with the component.

And what we found was some ligamentous strain and some reduction in motion, depending on whether it is varus, valgus, up, or down. And changing of the height of the mobile bearing.

But we haven't developed, that we know of, a very good testing device that would put the mechanical input into it. So it is up to be considered. It is not out of the realm of consideration. But it doesn't exist right now.

And I think that the incidence of

these problems is extremely small. Most of them were replaced or the bearing was replaced. And the patients did okay. And so it may not be as big a deal as it seems, I guess.

DR. PFEFFER: So test to failure using a static blow, I think that is the term, is a difficult thing here --

DR. SALTZMAN: Yes.

DR. PFEFFER: -- because if you look at the literature, not pertinent exactly to the STAR but if you look at mobile bearing ankles, such as a Buechel-Pappas, et cetera, and the Scandinavian literature from Europe, there is a four or five percent fracture rate of the PE component. So it is small but it's not -- I can give you --

DR. SALTZMAN: We think it is about one percent in our analysis.

DR. PFEFFER: In the STAR? From your group?

DR. SALTZMAN: From the Europe. I

can get the reference for you. It's here.

DR. PFEFFER: No, that's okay. All right. I think that answers the question.

CHAIR KIRKPATRICK: Dr. Skinner can also address part of that.

DR. SKINNER: I wanted to say that the failure in a static loading situation wouldn't be the prosthesis. It would be very unlikely. It would more likely to be foam interface.

DR. PFEFFER: Okay.

DR. SKINNER: So I don't think there is a place for a static load test here.

DR. PFEFFER: Okay.

DR. SKINNER: And I think that the fractures would be unlikely to occur in trauma -- fractures of the polyethylene anyway. It would be more likely to occur to fatigue mechanisms.

DR. PFEFFER: Good. Well, thank you very much. Thanks.

CHAIR KIRKPATRICK: Dr. Pfeffer,

any --

DR. PFEFFER: No, thank you very much.

CHAIR KIRKPATRICK: Thank you.

Dr. Propert, any additional questions or comments?

DR. PROPERT: I want to turn one of my previous comments into a question to follow up on something Drs. Mayor and Goodman said. First of all, I have had a couple of statistics courses but I grew up in the South.

MEMBER GOODMAN: Could you elaborate on those?

DR. PROPERT: So I don't know if I have any credibility here at all. But even as the statistician on the Panel, I don't want us to dismiss this aspect of clinical significance. By just quickly looking through the data here in the last few minutes, if I read it correctly, I think there was an observed 12 point difference in the overall BP score, three point difference if you take out

the range of motion.

And then on the safety issue, people were looking for a 15 percent non-inferiority margin for safety. So it would really help me if -- and this could be either for the sponsor or the FDA -- if people could talk a bit after lunch about why those are clinically significant differences.

And also whether 15 percent non-inferiority for safety is acceptable in this setting.

CHAIR KIRKPATRICK: Thank you.

Dr. Skinner, do you have additional comments or questions for the FDA or the sponsor?

DR. SKINNER: Yes, I'd like to ask one question. And it has to do with clinical issues. I want to make sure everybody knows that I am a clinician.

I was reading the article that was provided to the Panel by Anderson where he started doing total ankles in `93. And I

guess the question is are the surgeons in the U.S. inferior to the ones in Sweden? He was Sweden and was doing these total ankles, the STAR ankle, back then through an anterior approach.

And either the surgeons in the U.S. didn't learn from him the complications that occur or he didn't have the complications. Is it a question that the surgeons in the U.S. are just not as good?

MEMBER GOODMAN: Maybe at UCI.

(Laughter.)

DR. COUGHLIN: Dr. Skinner, we can't let that one go but I think Anderson's article deserves a much longer answer. And we have the analysis of that.

I'll say one thing. When we came here seven years ago, the point we got was that the European literature maybe wasn't trustworthy and that we needed to do our own study in America.

And if there is one thing this

fellow from Idaho learned was that you were right. That we really needed to get the data to find out what was true and what wasn't true.

When we come back after lunch, we'd love to talk about Dr. Anderson's article.

DR. SKINNER: Thank you.

CHAIR KIRKPATRICK: To clarify for the transcriptionist, that was Dr. Coughlin.

I think it would be great to hear that. Please don't plan on using all of the time after lunch to discuss that. But perhaps some bullet points would be very helpful.

Any additional questions, Dr. Skinner?

DR. SKINNER: No.

CHAIR KIRKPATRICK: I have one point of clarification I just want to make. I understood your answer to the deformity question as saying that you did no prospective analysis of the deformity. But in retrospect you had analyzed the failures and found many

of those had a deformity. Is that a correct understanding of what you presented?

It seems to me it would be a yes or no question by the people that did the study, not one that takes deliberation.

DR. SALTZMAN: It does seem that way. We did not do a careful retrospective study of all of our patients' preoperative deformity. We looked at the failures and especially the fractures, poly fractures, and looked at what they looked like.

CHAIR KIRKPATRICK: Thank you.

I would like to make a comment that is sort of an observation. And this may be more for future colleagues that want to come before the Panel.

But we have a litany of outstanding academic orthopedists in front of us working on behalf or in conjunction with the sponsor. And at the same time, we hear from our journals and from our meetings that we need to make sure that we establish our hypotheses at

the beginning of the study, stick with the plan, and make clear that if we do a post hoc analysis we don't mix the post hoc analysis with the presentation of the prospective study.

And in this study, it seems that we have made multiple variations from that. And so I would just encourage all of us to be making sure we stick to the tenants of evidence-based medicine when we come before the FDA as well as when we go before our journals.

And with that, I would like to see if there is any further comment from the Panel before we break for lunch.

Dr. Mayor?

DR. MAYOR: I have just one small but very specific clarification that either Dr. Popovic or the submitters might be able to clarify.

There was a slide which listed the surgical interventions in the pivotal study in

patients with surgical interventions of a number of different kinds, including mobile bearing removed and mobile bearing replaced.

And the question that I have is are those a summary of each other or are they inclusive of each other? And if either is true, exactly how do they sort themselves out? Do we add the numbers together? Do we merge the numbers together? Or do we separate them in some other imaginative way?

DR. POPOVIC: Actually the data originally presented included all the removals and replacements. Later on, the data was analyzed at the specific time point, 24 months, which means some of the replacements were not included because they occurred after the 24 months.

And that is why there was a difference in the slides. As a matter of fact, these changes came very, very late. As of last month. And, you know, we looked at the original data and presented the total

numbers. However, if you look at the cut off points, if you truncate the data, then obviously the numbers will be slightly different.

So 17 was the total. However, at 24 months, there were less than 17. And that's where the differences are.

DR. MAYOR: Thank you.

CHAIR KIRKPATRICK: Thank you.

Mr. Melkerson and Mr. Jean, is there any other Committee business that we need to handle before taking a break?

(No response.)

CHAIR KIRKPATRICK: Thank you very much. I know the sponsors will be very busy in preparing answers.

We would like to take a break for lunch. We will reconvene again in this room at 12:45.

Please be aware that if you have any personal belongings, please take them with you as the FDA staff -- excuse me, if the

public has any personal belongings, please take them with you because the FDA staff will be locked down in this room to make sure that it is secure.

And you will be allowed back in the room approximately five minutes before we reconvene.

Panel members, please remember that there should be no discussion of the PMA during lunch. And that goes with any member of the audience as well.

Thank you.

(Whereupon, the foregoing matter went off the record at 12:01 p.m. to be reconvened in the afternoon.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

12:50 p.m.

CHAIR KIRKPATRICK: Thank you, everybody, for returning so we can get the meeting back underway.

First I'd just like to see if the sponsor has any additional questions you'd like to pose before the Panel before we allow you to start your responses?

(No response.)

CHAIR KIRKPATRICK: I guess since there is no motion, there are no questions.

All right. Thank you.

Then is the sponsor prepared to begin answering the questions that were posed before lunch. And if you could please restate the question as you give the answers, I assume you have it organized in a way that you directly focused on the questions asked.

DR. COUGHLIN: Thank you, Dr. Kirkpatrick, yes, in the last few minutes, we have totally gotten organized.

I'm Mike Coughlin. And I want to start off with where I left off with Dr. Skinner's comment about the European study by Anderson. When I pulled that article -- and I first want to preface these remarks by saying that yes, indeed, this was a U.S. study.

The literature outside the world in other areas is questionable and we can glean some things from it but there are a lot of questions. This was the largest study that has ever been done. A prospective fusion study, arthrodesis study has never been done. A prospective ankle study of this size has never been done.

Now it was offered by the FDA that we just have pure meta-analysis but we felt that we should have a control with an arthrodesis group so that we would have some comparability with such things as Buechel-Pappas scores which, we thought, we could then examine function and pain issues.

Now this wasn't a perfect study.

And we grant you that. The control group was quite difficult. But it was a control group. And none of the other published studies have ever had an arthrodesis control group. It is tough to keep these patients in, as we have certainly mentioned to you.

Now in regard to Anderson's study, it is fascinating when we look at this and we look at the European history on this and then -- and I want to compare it to the American study that we have done here -- Anderson did 51 cases. And of those, 12 failed. Five went on to fusion and seven went on to exchanges.

In this article, there is no note of any inclusions or exclusions for criteria. And I think that damns this study to begin with. It really condemns it because that is the strong point of our study, I think. We really laid it out for inclusions and exclusions.

Instrumentation, he used some instruments that were only available to him.

They weren't company instruments that had been supplied to anyone else.

We don't know the trial sizes. He then came to the conclusion that he had a couple of poly breakages and took the big leap that you should not put six millimeter poly in but, in fact, he never said what size poly broke in this or his subsequent article.

So I used that as a jumping off point to talk about our study and the things we did right. We can find things that we can be criticized for -- the size of our control group, the follow ups, and so forth. And we admit that.

Now when we look at the two groups, and this was a question -- another question that was asked as far as how we picked the people who were involved. Now these were all top notch U.S. surgeons. And I think they are quite comparable.

It is hard to give a test on surgical ability or indications and

contraindications and to really read someone. But by reputation and by our personal knowledge, these were all good people. And they could have been either group.

The thing that really limited them as to which they went was their comfort with either doing a total ankle or doing an arthrodesis. And there were some very fine surgeons who would not take that leap and say I'm ready to put a total ankle in, remember the debacle of the 1970s. On the other hand, there were some people who were ready to make that move.

And I want also to recall again, for our American study, that the Waldemar Link Company had a choice here. They could have done a three-part study without a control in Europe. They could have just introduced the two-part ankle with the 510(k). But they took the road less traveled. They tried to do a much harder thing with our help.

I wanted to mention to Dr.

Pfeffer's question about the operative characteristics because we chose these surgeons not based upon if we thought we could put a stopwatch to them and measure how speedily they could operate. Their operative time didn't make much difference to us. We wanted results.

And I don't think that you can just jump from their operative time and say that this was a much more difficult or severe deformity. That is really not clear in the data that we have. It is an interesting question but it is certainly not clear to us.

And if you want to take that way of thinking, the results they got were superb. They have the best results, way better than any arthrodesis study that has ever been published in the literature.

Now we could have put some ringers in and got some mediocre surgeons. But that wasn't our plan. We had five people who were fine people who achieved excellent results.

Now having said that, again I want to reemphasize that the FDA offered us just a meta-analysis alternative but, indeed, we said let's do a control but we'll also do a concurrent meta-analysis evaluation.

There have been some questions regarding that as to did we cherry pick articles or how did we really come to the choosing of these specific articles because I think that is a very vital question. And I'd like Dr. Tom Clanton to speak to the meta-analysis process.

DR. CLANTON: My name is Tom Clanton. And since I've not been up before, I'll give disclosure. I'm a consultant for Link and paid for that and travel expenses. I have no stock options or equity interest in the company or other conflicts of interest.

In addressing the question of selection bias for the meta-analysis, that was raised previously due to the large number of articles that were excluded. So let me try to

explain this.

The original review of ankle arthritis literature went back to 1945 and included 73 articles. These were reviewed for complications in a total population of 2,090 ankle arthrodeses. In that group of articles, the non-union rate was 9.7 percent, ranging from zero to 35 percent. Malunion rate was 11.2 percent. Infection rate was 14.5 percent.

Summarizing the overall complication rate was 49.4 percent. That was the original 73 papers.

In order to define a population of cases that more clearly portrayed modern technique, a subset of 42 more current articles was evaluated. These papers were published from 1979 on.

And they included modern anesthetic agents, surgical technique such as compression screws and plates, and improved devices for external fixation. Also during that period,

we see the introduction of arthroscopic ankle arthrodesis and small wire fixators.

These 42 papers were quite diverse in terms of the patients included, sample size, surgical technique used, and outcome measurements. Therefore, for the meta-analysis group, the 42 papers were carefully reviewed and papers were excluded if they looked at a population of patients or a method of surgery that might be expected to have a worse outcome.

We purposefully biased the final 12 papers in favor of the arthrodesis group by excluding articles that included patients fixed by external fixators because we know that they have a higher infection rate from pin tract infections. We also excluded papers such as Popa and Meyerson's article on diabetics with neuropathy since that clearly would have had a higher complication rate.

So in looking at the 12 papers, they come from centers around the world,

including University Hospital in Nottingham, England, Nara University Hospital in Japan, Hospital for Special Surgery, UCLA. They include private practices in Seattle, Washington and Oakland, California.

They are a diverse population of patients from around the world. And they are primarily patients that would be included in the control population of patients, including diagnoses of rheumatoid arthritis, post-traumatic arthritis, and osteoarthritis.

They were all open techniques. We excluded all of the arthroscopic cases that were done. And they were done with modern surgical methods.

The complication rates for these 12 meta-analysis articles, in summary, was 11.6 percent where there was radiographic evidence of nonunion, delayed union, or malunion. And 11.9 percent device failure, revision, or removal. The overall failure rate was 17.4 percent.

In my opinion, this was a very unbiased method, given the overall poor quality that we know is present in the literature on ankle arthrodesis. We selected these papers, picking ones that were felt to be the best reflection of what would be the control population in our study.

And we did such things as in one case that included a salvage case for failed ankle replacement, it was kept in the study in order to use it as part of the denominator for complications because if it was removed, it would have effected the success rate negatively, biasing it against the arthrodesis.

We did that in two instances that could have been biased the opposite way. So I think that we did this in a very fair fashion. It would have been very easy to have chosen papers that would have had higher failure rates, would have included more patients that had worse outcomes.

And so I think that it is a very fair group to look at in the control population. And if you look at overall complication rates, it is less than any other population of 12 papers that would have been included.

CHAIR KIRKPATRICK: Thank you.

I would like to just alert both the sponsor and the Panel members to one aspect of the term meta-analysis and the application of that term. We may not be using it in the strictest sense of the word.

Many of the things I've heard sound like it might be a systematic review as opposed to a meta-analysis. So please, you know, keep that in mind. It doesn't sound like a strict meta-analysis was done but a systematic review.

I would also like to encourage the sponsor to recognize that they do have a relatively limited time to summarize these answers. We'd like you to focus on trying to

answer more of them with brief, to-to-the-point answers than trying to give us in-depth answers of each concern that we had. Now we'll give you approximately 20 more minutes.

Thank you.

DR. MANN: Thank you. Roger Mann from Oakland.

The question was raised by Dr. Pfeffer regarding the subtalar joint and its analysis. We know that the subtalar joint is extremely important in gait. It is part of a measurement of overall dorsiflexion/plantar flexion that occurs in what we call ankle motion but it also does include subtalar motion.

We also know that in patients with rheumatoid arthritis the subtalar joint is often effected. And as a result of that, there will be decreased motion in the subtalar joint.

One of the things we did notice in the study is that by preserving ankle joint

motion, we did not have any patients that progressed their subtalar joint problem or did it become symptomatic. So that is a plus for the STAR prosthesis.

Post-traumatic patients also have some stiffening of the subtalar joint. Patients with primary arthrosis usually do not. And I think that basically by doing an ankle prosthesis, we are sparing those joints.

Charlie Saltzman, in his articles, has shown that 20 years out, roughly a 70 percent incidence of arthritis of the subtalar joint as the result of the added stress as a result of an ankle fusion.

The next question was asked about osteophytes. At 11 months out, there were eight osteophytes in 158 patients or about a five percent incidence.

Next, this demonstrates a very large anterior osteophyte that occurred. What you are looking at here is -- there is the polyethylene. Here is the talar component.

And you can see the osteophyte coming along in this area right here.

This developed and blocked dorsiflexion of the ankle. This is the only one I found in the anterior aspect of the ankle joint.

Next, this is our typical picture of what you would tend to see, namely some osteophyte formation along the medial aspect of the joint, right through here. And this sometimes is symptomatic. Usually it is not symptomatic.

Next, looking at this clinically, this is what we observed when we opened the joint. You see a little osteophyte here but mainly osteophyte build up along the medial malleolus area. We take the polyethylene out in these cases in order to gain exposure to this area. And then you can see using a osteotome, we then will clean out this medial margin here and as long as we are there, we always take some bone off laterally because we

are orthopedic surgeons. We have to take bone out.

Next, this is sort of what it looks like after debridement. You can see now we've opened up the gutter on both sides. As far as from a clinical standpoint, these patients do quite well.

The only risk of the operation, you do have to enter the joint again through your anterior incision and pull out the poly, take off the bone. And these patients can walk immediately. And it takes them about three to four weeks to get back to their preoperative state. So this is what we found as far as osteophytes are concerned.

CHAIR KIRKPATRICK: May I just clarify? Are we using the same term osteophyte and heterotopic ossification?

DR. MANN: Yes, this basically is heterotopic ossification.

CHAIR KIRKPATRICK: Okay, you'll forgive me because when I was a resident, they

were very, very different things.

DR. MANN: In the ankle joint, I think they are the same.

(Laughter.)

CHAIR KIRKPATRICK: I'm sorry, so as a follow up now, then I have to rethink what is the HO incidence. You said five percent that needed operation?

DR. MANN: It was five percent out of 158.

CHAIR KIRKPATRICK: Okay. That needed operation.

DR. MANN: That's correct.

CHAIR KIRKPATRICK: Okay. And radiographically what was it?

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

CHAIR KIRKPATRICK: Thank you.

DR. SALTZMAN: All right. I just want to mention I think Dr. Mayor asked the question about the 15 removal/replacements. And I think among those -- we think nine of

them were replacements. And a number of them, maybe roughly that nine were just like this.

And the recovery, for those who are not clinicians, recovery from that surgery is two weeks, three weeks. And then they are fine. It's a little different than a real revision which the recovery might be two or three months.

We had not prepared x-rays on those who had settled. And some of the radiographs that have been brought up as part of the perhaps change in analysis of the radiographs, I wanted to talk to that. And Dr. Goodman brought that up and I know a number of other people brought this up.

And so were able to download off our email this one case, which is one of the cases that was -- one of the five cases that were reclassified as having not been radiographic failures. And I wanted to describe that for you.

So to give you some understanding,

the original criteria was to identify -- it is very important to identify loosening and migration of implants. And if we identify loosening and migration, we thought we should go ahead and call those failures.

We didn't have any real criteria for loosening and migration so I actually went through all the x-rays and measured the x-rays. And on these x-rays I would have measured that there was four millimeters or more settling of the talar component on the talus.

And it would have been most likely, in this case, I can't -- I'd have to go back and look at the sheets but mostly likely it would have been right in the front that that measures four millimeters of settling of the anterior part of the talar component into the talus.

Now for whatever reasons, the four millimeters was picked out as a cut-off point without any prior knowledge or data to

support it. And that became a failure. And was sent to the FDA as a failure.

And what happened was for this group, which was five patients after the clinicians behind me sat down and looked through some of the data -- and this is after the submission -- we realized that some of these patients that were considered radiographic failures might not be failures because they may not have progressed.

And so we went back and looked at the records on them. There were approximately 11 of those patients. Three were failed for other reasons. That gets us down to eight. Of those eight, three we felt were continuing to migrate so that got us down to five.

Those five had migrated in the first six months -- by the six-month or the 12-month x-ray. And they stopped migrating. So that at the 24-month x-ray, it was the same as the 12 -- I'm sorry I don't have the 12 to show you. And then we went ahead and looked

at their 48-month x-ray. And that is where we got into this 48 month piece.

And then to confirm that we had what we think is a clinical success, we went back and looked at the BP scores, the Coughlin scores, the SF-36, everything we could look at to see if there is any evidence that this might not have been a success. And for five patients, we feel that they were successful. So that's that reclassification.

I wanted to speak also about another reclassification I don't have an x-ray on but I can tell you and I think you can understand this very easily. The x-rays are susceptible to artifact with rotation of the leg compared to the plane of the x-ray beam. And because of that, sometimes the talar component in particular -- you can leave that up -- just leave it up because I think it is helpful to see an x-ray -- sometimes what will happen is the talus will look, because of its shape, and it is on a convex surface, will

look like it is invaginated or falling into -- the component has fallen into the talus.

And if that happens, since these were read independently and timed independently, I would have marked it as being greater than four millimeters migration so it would be considered a failure. Now what happened was for seven patients later -- say at six months we thought it was a failure and later, at 12 months and then at 24 months, we thought it was -- I marked it as normal.

Well, the fact is the implant can't un-migrate. It can't go back up. And so the original readings were wrong. And I'm sure of that because if you get a normal reading on a lateral x-ray like this that is perfectly positioned, it hasn't un-migrated to that position.

So that explains the seven and the five. And that's why we did this re-analysis of the data that brings the delta for safety -- it actually brought it up under the 15

percent. I just wanted to speak to that.

There was a question about why we didn't look at -- I think re-review the control x-rays, we probably could have done that it would have made the control group or the arthrodesis group probably look worse.

We had set three months as the point at which procedure becomes a delayed union. In other words, if you are not fused at three months, it is was a delayed union. We actually think that is a little severe. And we talked about it and we think four months might be reasonable.

At three months, 56 percent of patients are wearing casts. At four months, 13.5 percent of patients were still in casts so that would have been the delayed union rate. We didn't go back. We might have found a few more. We actually relied on the investigator at the site to tell us whether it was fused or not.

And so I think this speaks, I hope,

to Dr. Propert's question did you use 48-month data to tell you how patients were doing at 24 months, we did not do that. I want to make sure that is perfectly clear.

And I believe I tried to answer all those question.

The wear and the explant questions, we have Paul here from the ORL who will try to answer some of those better than I could.

Thank you.

MR. POSTAK: Thank you. My name is Paul --

CHAIR KIRKPATRICK: Excuse me just one second. There is quick follow up question with regard to what was just said.

MEMBER GOODMAN: Thank you for those figures. Do you have any other figures before 24 months on this case or in any other cases where there was translation or migration of any of the components?

DR. SALTZMAN: We do. I don't think we have them on our computers here. We

can look through our emails and see if we can find it. Sorry we didn't bring that.

CHAIR KIRKPATRICK: Thanks.

Go ahead.

MR. POSTAK: Hi, I'm Paul Postak from the Orthopedic Research Laboratories in Cleveland, Ohio. I have 22 years experience in biomechanical device analysis and in hips, knees, shoulders, elbows, wrist, spines, and, of course, ankles.

Today I am a consultant for the sponsor for which I will receive my expenses and travel covered. In addition, testing done in the preclinical phase at my laboratory was done on a one-time fee for service basis.

The sponsor had no control over which results were presented with very limited control over what the protocol was for the analysis.

I have no equity in any medical device company. And I have no royalties assigned for any medical devices.

I plan to cover two questions, the first question involving some of the packaging for the polyethylene components. The polyethylene for these mobile bearing devices was packaged in an oxygen-resistant barrier in nitrogen and then sterilized at 27 kiloGrays.

The storage limit on these devices is five years for sterilization and alleviate the storage oxidation questions.

I know this packaging is identical to all of Link's polyethylene components used for hip and knee devices throughout the world. And I know of no failures or any links to any failures associated with this packaging nor this packaging technique.

And in addition, it is quite a standard practice of the orthopedic industry.

Does address your question concerning --

DR. MAYOR: It's been proven in the past that many standard practices have been ill advised. And the reason I raise that

issue is that now increasing evidence is accumulating the you may be able to prevent on-the-shelf oxidation with barrier packaging.

As soon as that package is open if a population of free radicals is present in the polyethylene, it will start to oxidize. We have been reassured, I think inappropriately, that the oxidation rate may be so slow as to be insignificant in the long run.

We are actually accumulating evidence as we speak that that is not an adequate reassurance. And so a further question that I would raise in specific regard to your laboratory is what protocols would you apply to a received retrieval polyethylene component to identify what its oxidation levels and mechanical properties might be at that point?

CHAIR KIRKPATRICK: Just briefly for the transcriptionist, that was Dr. Mayor.

MR. POSTAK: Certainly we would be

very interested in that type of research. However, the retrieval analysis for these devises was again not part of the original section. There were quite a few controls that were not maintained for the devices as they were retrieved and sent to our laboratory.

I've had an opportunity to schedule a retrieval analysis in other devices that would alleviate some of those issues and allow us to analyze whether any of the packaging effects could contribute to device failure.

DR. MAYOR: Which is certainly appropriate. But I'm still less than perfectly reassured. Do you have a protocol that you either have in place or are going to put in place so that you can make a more exacting assessment of both oxidation levels and/or mechanical properties for these retrievals?

MR. POSTAK: There is no explant protocol that I know of for this device.

DR. MAYOR: Well, I can suggest

that we have one.

CHAIR KIRKPATRICK: I believe there is also an ASTM standard to explanted orthopedic implants.

DR. MAYOR: Yes, there is. There is a retrieval analysis process that ASTM has described. I'm not sure that it is as rigorous as we would like to see it but that is characteristic of a lot of ASTM documents.

CHAIR KIRKPATRICK: Well, my point is that somebody dealing with orthopedic implants should be aware of these issues and be proactively addressing them as opposed to coming to a Panel meeting and saying oops.

DR. MAYOR: Well, said.

CHAIR KIRKPATRICK: Thank you.

I wish to remind the sponsor that you have not yet addressed BMI versus weight, range of motion, the death questions, and the post-approval x-ray questions and you have approximately five minutes. Thanks.

DR. COUGHLIN: I would like to the

death questions. There were four deaths in this study. One was from a pulmonary embolism one week after surgery. Three months after surgery a gentleman died of a myocardial infarction. At fifteen months, metastatic disease claimed another patient. This was not diagnosed at the time of his surgery. And a fourth patient died of congestive heart failure and pneumonia.

We believe that none of these were directly related to the implant itself.

I would like to briefly talk about the 50 percent delta that Dr. Propert mentioned. And that was agreed to by the FDA at the beginning of the study. I agree that ten percent would have been probably more common and more likely. But it would have required a much larger sample size. And, as you know, we had some difficulty enrolling the arthrodesis group. And it would have made a much longer study, probably doubling the size of the arthroplasty group itself.

I think also that when we talk about the satisfaction scores that you mentioned, you said that you saw the similar level for both the arthrodesis and total ankle groups. And I agree with that. That non-validated score was used. I actually invented it many years ago.

But if you only know one thing and you only have a fusion, you don't know what anything else is like. Likewise, if you only have a total ankle, then that will be your level of satisfaction. Our people were equally satisfied though.

Now I want to just talk about the clinical significance or statistical differences. There is a big difference in the range of motion when we are all done. About seven points different in those two groups. And I think that is important.

Pain, it was -- you know that's the goal for arthrodesis. But, in fact, we were the same for pain relief in both groups.

And I think that if you look at the consistency of all the way across the Buechel-Pappas scores, the BP function scores, that really tell you the story.

Clinical significance, you know, I'm not a statistician. I'm a clinician and an orthopedic surgeon. And when I see my patience, here is the difference. They can walk up a slope. A fusion patient can't.

Can they wade in the river on cobblestones and fish? No, they can't. Can they ride a bicycle? It is harder if you have an ankle arthrodesis. Can you climb stairs? One at a time if you have an arthrodesis.

So these numbers, when you really come down to it, the BP scores sort of tell us about function. They tell us about pain and other issues. But it is the function of the patient that really gives us the real answer in the long run.

DR. COUGHLIN: I can try to answer a few of these questions, BMI versus height.

Can you rephrase the question, Dr. Pfeffer?

DR. PFEFFER: Which do you plan on using in the future and which do you think is more appropriate?

DR. COUGHLIN: I personally think the weight is more appropriate. That is what is going to go through the prosthesis. The BMI is your weight divided by your height squared and gives you sort of a sense of the relationship between what is inside and what is inside basically. And I don't think it fits.

And I think you brought up a very good point that the implants have to fit the skeleton. If the implants are too big or too small, they are not appropriate. But I think weight is a better marker. That's my own opinion.

The second question, just to move down, was the subtalar range of motion question. And, again, we didn't measure that. It is very important to the function, as Dr.

Mann has said. It may have had some impact.

We would suspect that in our group that has actually 20 percent -- the group that is the experimental group had 20 percent rheumatoid and the other group had maybe about seven percent rheumatoid less, less rheumatoid patients -- the group that got the STARs would have worse, in general, subtalar motion because they are more likely to have multiticular involvement.

So we would say, if anything, the results are biased against the STAR group for motion. But we didn't measure that and it is a strong and very good point.

The last question which was I think the continued access x-ray question was mentioned. I'll try to be quick on that. When the sponsor was asked by the FDA to get some information on x-rays --

CHAIR KIRKPATRICK: Excuse me, if I could just clarify, it is for post-approval plans.

DR. COUGHLIN: Oh, post-approval, okay. It's not that. There was an amputation, too. But she's going to do that, okay.

DR. AHRENS: And I have it.

DR. COUGHLIN: The post-approval plan is to get standing x-rays, AP lateral of the ankle pre-op, one year, two year, four year, and eight year. We think those intervals will tell us if the implant is migrating and if we have a problem. So zero, one, two, four, eight. And we think we probably can get the patients to come back at those intervals.

CHAIR KIRKPATRICK: On all patients?

DR. COUGHLIN: On all patients, yes. That's right.

CHAIR KIRKPATRICK: Thank you.

DR. PFEFFER: May I ask for a clarification at this point? Or should I want until later?

CHAIR KIRKPATRICK: Go ahead and ask.

DR. PFEFFER: I just really need to clarify a point. If you look at the pivotal group and if we look at those who had, on the Buechel-Pappas score, less than 14 degrees of cumulative motion in the hindfoot, that's a really stiff hindfoot, Dr. Coughlin has already said this is ankle but it probably is some kind of cumulative -- it's on page 25 -- I don't know where in the book, okay.

Now the arthrodesis group had a 53 percent -- 53 percent of the arthrodesis group has less than 14 degrees of hindfoot motion while only 27 percent of the STAR group did.

Now we all know that the stiffer the subtalar joint, which is probably implied by that 53 percent, the worse we are going to do after an ankle fusion. So the division of these groups is not biased in favor of the STAR but it is highly biased in favor of the ankle fusion group doing poorly.

Would you agree with that? You know these patients. I just see the data. Just look at page 25 and look at your range of motion. Do you see? You have a much stiffer group in your arthrodesis group which I would expect would do poorly.

CHAIR KIRKPATRICK: Dr. Mann?

DR. MANN: Dr. Mann. Well, what you say is correct. But these people do have enough range of motion that they can get by with it. If the subtalar joint was that deteriorated prior to surgery, we wouldn't have put them into the study as we would have excluded them from the study.

DR. PFEFFER: But you don't feel that this has biased the arthrodesis group to do poorly because patients who were getting arthrodeses had worse subtalar motion in the STAR group. Forget the STAR. Let's just look at the ankle fusion group.

DR. MANN: Right.

DR. PFEFFER: As I look at all the

data, this bit of data is the part that stymies me. Because clearly depending on how well the ankle fusion group does reflects on the STAR. Fifty-three percent of the arthrodesis group versus only 27 percent of the STAR group had hindfoot motion of less than 14 degrees.

DR. SALTZMAN: Is that total range of motion? It's not hindfoot motion. It's total --

DR. PFEFFER: I'm taking -- no, what it is called is combined motion.

DR. SALTZMAN: It's probably ankle --

DR. PFEFFER: Yes.

DR. SALTZMAN: -- subtalar, talar, talonavicular joint --

DR. PFEFFER: Right.

DR. SALTZMAN: -- motion. And so the problem with that analysis, I believe, is you can't --

DR. PFEFFER: My analysis?

DR. SALTZMAN: -- say that the subtalar joints were stiffer in one group than another because you are combining an ankle joint that is invariably stiff in that total range. The other thing is, as you know, to be fair to the non-clinicians, measurement of motion around the ankle is very difficult clinically. And we think there is quite an error in that motion.

DR. PFEFFER: All right. I think that is a fine answer. Had you used your criteria, the Saltzman criteria, that Pyevich used with the Agility ankle, we wouldn't have this problem because you would have range of motion documented by x-ray.

CHAIR KIRKPATRICK: If I may, we're not going to get into a debate on all that.

DR. PFEFFER: Sorry.

CHAIR KIRKPATRICK: But I would like to reiterate the fact that in my training, we had a very esteemed senior faculty named J.L. Goldner and he used to talk

about evaluating subtalar motion by its imperceptible but I can feel it. So that's something that we all need to keep in mind.

On a follow up to the range of motion, however, did you get radiographic range of motion studies? Pre-, post-op, anytime?

DR. COUGHLIN: No, in general we did not. We had started, as I mentioned earlier to another question, we started to do that and then the harangue from patients and doctors about if we were checking range of motion at, you know, six months, year, so forth, with extra x-rays, we clinically or we just morally couldn't do that.

I mean I wanted to do that because I wanted to prove it and to show it. But my --

CHAIR KIRKPATRICK: The answer is no, thank you.

Did you have another response?

DR. AHRENS: Yes.

CHAIR KIRKPATRICK: Please identify yourself for the transcriptionist.

DR. AHRENS: I'm Jeanette Ahrens.

First I'd like to point out that Slide 39 in the FDA presentation we realize is -- there is an error in it. We discussed this with Dr. Foy during the break. Really it actually is -- the title states that it is overall success but it is really safety success.

And then this slide seems to indicate that we didn't meet our overall success rate, however, in fact, we did our overall success rate with all analyses in both pivotal and the continued access studies. And so we just wanted to state that for clarification. Our Slide 96 actually shows this slide corrected.

In addition, I would like to answer some of the statistical questions. First, the easier one.

Dr. Pfeffer, regarding the protocol

exemptions, the osteoporosis and the weight, those patients were included in both the ITT and the completers analysis. So they weren't included in the protocol but they were included in the other analyses.

Okay, moving on to the other ones, the continued access safety success rate where we actually looked at the comparisons, when we compared the safety success rate in regarding the radiographs to the pivotal and the control, we did four different analyses regarding that.

The first one we compared all groups without radiographic data. We wanted to go ahead and make sure that we had everything cross-comparison.

The second one, we did all groups with radiographic data that was available, even for the continued access patients.

The third one was an imputation where we applied the radiographic failure rate alone. That means those patients that

presented as radiographic failures that were also not considered major complications or had surgical interventions in the study at that time period from the pivotal study to the continued access patients that did not have radiographic data.

We did this for both the original PMA analysis as well as the revised analysis on the radiographic data.

All the findings from these imputations in the various analyses that we did in these four different areas were similar and all demonstrated non-inferiority with the control group compared to the continued access.

There was a suggestion that there was interim analysis that was performed because we had three patients that were actually not completed in the arthrodesis group to their 24-month window. We don't believe that this was an interim analysis because we are missing three patients. We

weren't assured that we were getting those three patients away.

We did take measures to impute the missing data in both worst case analysis and the last observation carried forward. So I just wanted to go ahead and clarify that.

And the final statistical issue was regarding the propensity-adjusted scores. It is important to note that despite their limitations both the propensity-adjusted and covariate-adjusted analyses that were performed did not change the conclusions from the unadjusted analyses.

We acknowledge that with the differences between the groups and that may exist in variables that were not collected. Therefore, the propensity and covariate analysis cannot adjust entirely for the differences between the groups.

But as Dr. Coughlin has stated, a study of this magnitude has not been attempted before in the ankle and the clinical

significance of these results and differences should be considered as they were addressed by the clinicians.

Thank you.

CHAIR KIRKPATRICK: Thank you.

Okay, we're going to have a comment from the FDA with regard to the slides on the statistical analysis. Go ahead, yes. I'm just mentioning that is what you are going to do.

DR. POPOVIC: Yes, hi, I'm Dr. Popovic. I presented the Slide 39 and I'd like to point out that all the slides that we presented were presented and given to the sponsor as of last Friday. This is the first time I have heard any comments about Slide 39.

I would also like to point out that just about on a daily basis we have gotten re-analysis of the data, ad hoc analysis --

CHAIR KIRKPATRICK: Thank you. I am equally as frustrated as you are at the lack of attention to detail when it comes

across. But I don't think now is the time to address that.

DR. PROPERT: But I just want to point out that there is a possibility that the title may be slightly different. However, I want to suggest that the time for correction was earlier on --

CHAIR KIRKPATRICK: I agree but we need to move on. Thank you.

Mr. Melkerson?

MR. MELKERSON: I apologize for that. But in terms of discrepancies in one or two numbers, it is not an issue here. I would leave the Panel to the discussion.

CHAIR KIRKPATRICK: I concur. Thank you.

I do have one other follow-up question on the desk. I didn't catch the time of the MI. You said there was a myocardial infarction.

DR. COUGHLIN: Yes, sir, three months following the surgery.

CHAIR KIRKPATRICK: Three months following surgery, was that a rehab event? Or was that simply an isolated event not related to their rehab?

DR. COUGHLIN: I'm not aware of that.

DR. AHRENS: A related prior condition.

DR. COUGHLIN: A related prior condition.

CHAIR KIRKPATRICK: Thank you.

I would suggest to the Panel that a PE anytime within the first three months after surgery is related to the procedure. But my interpretation would be we would have to question whether it was related to the implant. And in my clinical judgment, it probably is not.

But it is -- as advice to everyone in the room -- it is a reportable event because we don't yet know whether it could be specifically device related. Thank you.

Are there any other questions from the Panel that we did not get addressed? Anything that we asked before lunch that we didn't hear adequate answers? Are we okay?

Dr. Propert?

DR. PROPERT: And thank you, the statisticians, for those clarifications.

This may have been answered and I missed it but I'm still unclear on whether the control group underwent the same review of radiographs. I realize the criteria are different but if the exact same level of review was done for the control subjects. It has been brought up a number of times.

DR. COUGHLIN: No, you bring up a good point. The radiographs were reviewed by the site principle investigator for the control groups. There was no central reviewer. They were not re-reviewed.

DR. PROPERT: They were not re-reviewed.

DR. COUGHLIN: We relied on the

reading of the clinical investigator whether the ankle was fused or not. And whether it was fused straight or crooked.

DR. PROPERT: Okay. Thank you.

CHAIR KIRKPATRICK: Thank you.

Are there any further clarifications of our questions that we asked the sponsor or the FDA before lunch?

(No response.)

CHAIR KIRKPATRICK: Seeing none, thank you.

At this time we'd like to focus our discussion on the specific FDA questions.

Mr. Pinder, I understand you have some slides prepared to go over -- the FDA questions.

Yes? And would you please begin by reading Question No. 1?

DR. SALTZMAN: Could I clarify one thing? I just wanted -- for those who are not clinicians, we think that most orthopedic surgeons know how to read an x-ray for a

fusion. And that any foot and ankle surgeon should be able to do that. And that is why it wasn't read centrally.

We may have under -- we may have had more non-unions if --

CHAIR KIRKPATRICK: Thank you.

DR. SALTZMAN: -- we had read it.

CHAIR KIRKPATRICK: Thank you. Yes, that's a methodological issue that -- thank you.

Mr. Pinder, at this time, we'd like you to address us with Question No. 1.

MR. PINDER: All right. Panel Question No. 1, the applicant has revised the pivotal radiographic analysis that was initially provided in the PMA. This revised analysis impacts a total of 12 STAR patients, seven patients who did not meet the original analysis definition of success at six or 12 months into a radiographic success at 24 but were carried forward as radiographic failures, and five patients who were radiographic

failures but who were considered clinical successes and who did not have radiographic progression.

Under the original PMA protocol, the 15 percent non-inferiority margin delta for safety was not met. The delta is met by including these 12 patients as safety successes.

Please comment on the appropriateness of the revised analysis and the impact of these changes on the interpretation of the patient safety and overall safety success rates for the study.

CHAIR KIRKPATRICK: Thank you.

We'll go around the table but we will start at different people for each question. The first one we'll start with Dr. Mayor.

DR. MAYOR: Thank you.

In response to Question No. 1 addressed to the Panel, appropriate? No. Adequate? Probably. Impact? None.

CHAIR KIRKPATRICK: Thank you.

Dr. Pfeffer?

DR. PFEFFER: Are you reading from something?

(Laughter.)

DR. PFEFFER: All right. I think the Part A is completely reasonable. And I think in terms of study design, although I'm not pleased with Part B, it is acceptable to me given the attention to detail that they placed. And I would allow those patients to all be considered as part of the statistical analysis.

CHAIR KIRKPATRICK: Thank you.

I'll remind the Panel members that there copies of the questions in our blue folders. So you are not forced to see me after the Panel meeting for your cervical radiculopathy. If you'd like to look at it in front of you, you have it there. Thank you.

Dr. Propert?

DR. PROPERT: I agree with Dr.

Pfeffer that A is not a problem provided there is no clinical information in people who improved between 12 and 24 months.

I do think B is an issue. I can't really assess the radiographic criteria but it always worries me when a decision or a conclusion about the effectiveness of a treatment hinges on five people.

CHAIR KIRKPATRICK: Thank you.

Dr. Skinner?

DR. SKINNER: Well, these are clinical studies and clinical studies have problems. And if you knew exactly what was going to come out of them, you could design them perfectly.

And I think that this is reasonable, perhaps not appropriate, but certainly reasonable.

CHAIR KIRKPATRICK: Thank you.

Dr. Goodman?

MEMBER GOODMAN: Well, I think definitions are really important. I don't

think you can talk about radiographs and talk about clinical success in the same mouthful. I think the best of all studies makes definitions before the whole study starts and sticks with them.

And I can understand the dilemma that the investigators found themselves in, that some of the patients who probably had radiographic failures, so to speak, were doing clinically all right. But I think one should use the terminology that one chooses at the beginning rather than modify things as one goes along.

CHAIR KIRKPATRICK: Thank you.

Dr. Wright?

DR. WRIGHT: I agree with everything that has been said. I think that in reference to B, I think that we would call that a stable radiographic failure. It's not progressing. It is staying the same.

I think we would really have problems if we didn't like the alignment of

something, that it was not radiographically satisfactory versus something that is in satisfactory alignment but has a radiolucent line. So I think the explanations were adequate.

CHAIR KIRKPATRICK: Thank you.

Ms. Whittington?

MS. WHITTINGTON: I concur, especially with Dr. Goodman. But we have many well-educated consumers and if they see that Part B does not meet the radiographic failure definition, I think that that would raise their eyebrows. And we have a lot of very educated patients these days.

So it can be a clinical success. I understand that and I've seen it. But I think that needs to be clearly delineated. I have problems with B.

CHAIR KIRKPATRICK: Thank you.

Ms. Adams?

MS. ADAMS: Well, I appreciate the comments of the rest of the Panel, especially

the ones that talk about the practical side of this. Coming from industry and having been a participant in a variety of different kinds of responsibilities associated with these sorts of studies, this issue of radiographic success and failure is an ongoing issue in the orthopedic community.

We see it in spine studies. We see it in almost every study that somebody tries to prepare. And the FDA is trying to do a good job by helping us sort through defining objective criteria.

And companies are trying to sort through what they should look like. But this is not new what this company is experiencing. And it is not unusual. So I sympathize with them for the struggle that they went through on this.

CHAIR KIRKPATRICK: Thank you.

Mr. Melkerson, in summary to that question, the purists in us would say that it was inappropriate, however, a realistic way to

look at the data.

And as far as whether the radiographic failures and clinical successes or radiographic success correlates to clinical failure or clinical success we would say we don't know. Does that adequately address this question for you?

MR. MELKERSON: A point of clarification and I think I've heard a couple of things, in terms of how radiographic success was defined, some of it was in terms of subsidence, some of it was in terms of angulation or orientation. And I thought I heard that if the issues of alignment come into play, we may have a little bit different concern with that.

How would you suggest labeling something should that -- now you talked about clinical success and radiographic successes being different terms, but how would you suggest the FDA approach something like that in terms of labeling?

CHAIR KIRKPATRICK: I'm not sure I know exactly what you are getting at.

MR. MELKERSON: You have defined a clinical success or radiographically stable in terms of presenting information and we have already identified the user community wants to know what does that mean to me as a patient. How do you present that information in terms of do you split out radiographic from success? Or do you combine them?

CHAIR KIRKPATRICK: I would suggest that I'll take a first stab at that and say that you would need to have in the labeling a presentation of the issues separately so that the surgeons and/or the patients can make their own decision as to whether that was a success or not.

And I'll certainly open it to other Panel members to comment.

DR. WRIGHT: Since I got us into this by talking about -- the flip side of this coin is that we really didn't talk about the

radiographic analysis of the fusions. And so I think, you know, I was just trying to define what a stable radiolucent failure could represent. But I think that the explanation was satisfactory.

CHAIR KIRKPATRICK: Any additional answers about labeling?

(No response.)

CHAIR KIRKPATRICK: Thank you.

Then does that adequately address Question 1?

MR. MELKERSON: I believe so.

CHAIR KIRKPATRICK: Thank you.

Please proceed with question two.

MR. PINDER: All right. Question two, fractures of the mobile bearing have been noted in the applicant's informal retrieval analysis. Fractures have also been reported in the literature.

Functional wear testing performed by the applicant has not replicated this clinical failure mode. The compressive load

used during testing is less than half of what the Agency considers worst case.

Though fracture rates are relatively low, please comment on the adequacy of the functional wear testing and please discuss whether any additional preclinical testing would be helpful to address long-term device durability.

CHAIR KIRKPATRICK: Thank you.

This time we will start with Dr. Pfeffer.

DR. PFEFFER: Well, this is perhaps the area of my least expertise but as Dr. Saltzman said, the understanding of the biomechanics of the ankle are in its infancy. And this ankle is being recommended for people up to 250 pounds.

I'd like to see this ankle placed through 10 million cycles at 6,000 Newtons so we can gather as much information as possible which I understand is not a particularly onerous thing to do and is possible.

CHAIR KIRKPATRICK: Thank you.

Dr. Propert?

DR. PROPERT: I'll abstain on this one.

CHAIR KIRKPATRICK: Thank you.

Dr. Skinner?

DR. SKINNER: Dr. Propert, how many samples did you say?

DR. PROPERT: I would defer on that -- 2,000 samples? No, I'm joking.

(Laughter.)

DR. PROPERT: Your call, Harry.

DR. SKINNER: Well, ten million cycles is several days testing if you just do it straight through. But I'm not sure -- I certainly think that the fractures are concerning and I'm not sure they are related to the wear testing.

If it appears from the retrieval set that have been obtained, and that data wasn't available to us, that it is related to the metal markers that are placed in the

polyethylene, three of which broke in the wear testing, then I would say that further wear testing would be appropriate.

And if further wear testing was going to be done, I think it would be appropriate to do that wear testing at higher loads. Not necessary 6,000 Newtons but certainly at loads that would be more appropriate for these large patients that it is apparently indicated for.

I think other than wear testing, I think that perhaps more information could be obtained from further FE analysis to look at stress levels in areas where fractures seem to initiate in the polyethylene. And that's relatively easy to do and could be very edifying.

CHAIR KIRKPATRICK: So if I could clarify, you would suggest that they review the fractures that have occurred and see if they can look at that with the finite element model to determine the mechanism?

DR. SKINNER: Yes.

CHAIR KIRKPATRICK: Thank you.

Dr. Goodman?

MEMBER GOODMAN: I'll be brief. I think that more realistic biomechanical studies should be done in the patient populations dictated by the indications. So that would be heavier patients certainly. And those could be negotiated with the FDA.

Second, I think we heard about an opportunity to look at the retrievals for any operations which have gone on to revision. And this may also shed some light on the mechanisms of wear and possibly the mechanisms of fracture as told to us by Dr. Skinner.

CHAIR KIRKPATRICK: Thank you.

Dr. Wright?

DR. WRIGHT: I agree. I think that probably a realistic approach might be to adopt a universal retrieval analysis of these implants because I had a very poor feeling for where the implants were fracturing.

CHAIR KIRKPATRICK: Thank you.

Ms. Whittington?

MS. WHITTINGTON: I have nothing additional to add.

CHAIR KIRKPATRICK: Thank you.

Ms. Adams?

MS. ADAMS: Nothing further.

CHAIR KIRKPATRICK: Okay, thank you.

If I could just ask one thing that I anticipate Mark will ask, do you believe that such additional testing should be done before approval? Or as post-approval within a certain amount of time? Or anything like that? Oh, I'm told that this will come up if we get to the vote anyway. So keep that in mind, okay? Thank you.

Mr. Melkerson, it sounds like -- oh, I'm sorry, you are right. I didn't keep my order, so Dr. Mayor. Thank you.

DR. MAYOR: Thank you. My perspective on this issue is that we are

dealing inappropriately with the question of testing. And the reason I say that is that I think we need to be very clear about what it is we are testing.

We take a polyethylene bearing, which has never been sterilized, has been managed very carefully through the manufacturing process in fabricating to its final form, we can test that and not represent in any remotely reassuring way what an implant that has been sterilized, packaged, stored in a detail person's vehicle through the summer in Georgia. And then brought in to the operating room on request, opened, implanted, and then walked on for four years. That piece of polyethylene is not the same.

And so unless we make that distinction, we are not going to get an answer from any regimen of testing to the question that we really need to ask. And that is how durable is the polyethylene that has been carried through the entire process to

implantation going to be three or four years later after a patient of whatever size has been making demands on it.

So I remain very concerned about the mechanical durability of these polyethylene components in this design element where we are dealing with a 48-month cadre of a segment of the studied population in the context of a situation in which four of them fractured and was described, at least for a small number of those fractured components, that they were traumatic in nature, my sense of polyethylene and lower limb biomechanics regarding biological tissue is that trauma that was severe enough is going to damage the bone first and the polyethylene either not at all or later.

My concern is that a polyethylene component that fractures under that kind of traumatic load has lost some of its original mechanical properties. And in view of testimony to that loss of mechanical

properties that is evidenced by the fact that it fractured, it's very troublesome.

I don't know how many of the European studies would address the question of long-term durability beyond four years. But we certainly had evidence from the retrievals that we have looked at the Engineering School at Dartmouth that polyethylene bearings like the ones in the LCS meniscal bearing knee start to fail late.

They fail from catastrophic mechanisms. The tibia is no longer capable of supporting the superimposed femur. And the femur falls off the tibial meniscal bearing because it breaks.

And I don't want to see that repeated in any significant number of patients in whom expectations of at least a five- to ten-year durability in service was expected in that patient.

CHAIR KIRKPATRICK: May I just follow up with you, Dr. Mayor? Do you have a

specific way to determine that long-term durability?

DR. MAYOR: Yes. Implants that have been two years or more subsequent to their implantation should be evaluated for FTIR oxidation levels and mechanical properties, including elongation and ultimate strength.

And if those properties of ultimate strength and elongation are maintained and if the FDIR data suggests a level of oxidation below threshold, which we can identify quite clearly from our studies, then I would be reassured that the polyethylene is probably not an element of vulnerability in the ankle.

CHAIR KIRKPATRICK: So that, by necessity, requires retrieved implants?

DR. MAYOR: You could do it with manufactured implants that have been carried through sterilization. And those could be acceleration aged in order to demonstrate the effects of oxidation on their mechanical

properties.

CHAIR KIRKPATRICK: By various standards in the literature as far as that aging?

DR. MAYOR: Right. The technology is widely available.

CHAIR KIRKPATRICK: Thank you.

Dr. Skinner, you wanted to comment to something Dr. Mayor said?

DR. SKINNER: Well, I certainly agree with Dr. Mayor that the mechanical properties of a polyethylene implant are a function of the chemical environment it has been in for the past one, two, three, four, et cetera years.

But I'd also submit that the properties are a function of the mechanical environment it has been in. And that's why I have suggested the FE studies and perhaps more wear testing because those are something that can be done immediately. And get some information about what kind of mechanical

stress state it is going to experience in the coming years.

CHAIR KIRKPATRICK: Dr. Mayor, once again?

DR. MAYOR: I think you are quite right, Harry. But I still feel that we have got to be very clear about the fact that you may be dealing with two different populations of polyethylene, related to the time-related effect of oxidation, which we have been sobered to realize may not be available in terms of apparent change in less than two years of clinical service.

And that is why I suggest we can achieve insights that are necessary to reassure us if existing implants are brought in, having been processed the way clinical implants would be, and then accelerated aged to make sure that we are actually looking at performance-related responses of polyethylene components in the mechanical environment that the patient is going to expose them to.

CHAIR KIRKPATRICK: Thank you.

Mr. Melkerson, it appears that the Panel does have some concerns about additional preclinical testing that could be considered from two standpoints. One is the long-term durability and/or wear. And the second is the fracture which may be related to a long-term wear situation or may be related to some other aspects, either acute trauma or a fatigue fracture or whatever. But that is not clear yet.

Further investigation to replicate that mechanism may be of benefit. The specific methods of determining durability are apparently under debate. There are some quicker ways to do it with finite element modeling. But then there is also very relevant concerns about the long-term effects of oxidation on the polyethylene and its change in mechanical properties.

So does that adequately address your concerns on this question?

MR. MELKERSON: I believe so. And I think you for the discussion.

CHAIR KIRKPATRICK: Thank you.

Next?

MR. MELKERSON: All right, Question No. 3, the continued access study consisted of 424 patients. At the time of PMA submission the applicant indicated that 320 patients were expected for 24-month follow up. Information was collected on 211 subjects, 66 percent.

The applicant conducted a radiographic review on subjects that included in the first a continued access cohort, 150 patients. One hundred and twenty patients had a 24-month visit included in the database, 85 patients had radiographs digitized and available for analysis. And 80 radiographs were ultimately reviewed.

Please discuss whether the data available from the continued access study cohort are adequate to determine if the safety success rate is comparable to the control

group.

CHAIR KIRKPATRICK: Thank you.

Dr. Propert?

DR. PROPERT: This really is one of my major concerns. A 66 percent follow-up rate is pretty low. And if you look at the follow-up rate for the radiographs, depending on what you use as a denominator, I'm getting something between 20 and 66 percent.

And given our discussion two slides ago about radiographic criteria, I think we would need the data to actually put some solidity behind that statement.

Just another comment that if all the discussion I have understood about the learning curve is true, further follow up should actually improve the safety outcomes for the more recent subjects, I would think, overall.

CHAIR KIRKPATRICK: Thank you.

Dr. Skinner?

DR. SKINNER: Well, again, this

sort of goes to question one. I sort of recognize that clinical data has flaws in it. And you can't have a perfect study. I don't think this is necessarily the optimal way to go about this but I think it is probably adequate.

CHAIR KIRKPATRICK: Thank you.

Dr. Goodman?

MEMBER GOODMAN: Well, we have a dilemma. We have a large group of patients and not a lot of them have the follow up that we would like. And I'd have to rely on my statistical colleague to make a final judgment as to whether this is adequate or not.

CHAIR KIRKPATRICK: Dr. Wright?

DR. WRIGHT: I think that the follow up is adequate marginally. But I am satisfied with the results.

CHAIR KIRKPATRICK: Thank you.

Ms. Whittington?

MS. WHITTINGTON: I'm going to have to defer to the statistician on this.

CHAIR KIRKPATRICK: Thank you.

Ms. Adams?

MS. ADAMS: I would only comment that many PMA studies typically have enrollments of around 250 patients and we are making decisions about safety. And in this case we have 600 cases and we can debate all day long about radiographic success.

But I think if we had 600 patients enrolled and had a safety problem, we would see a signal. So maybe just to put it in context, that is my comment.

CHAIR KIRKPATRICK: Thank you.

Dr. Mayor?

DR. MAYOR: I think it represents a classical quandary in clinical experimentation where follow up is hard to get without the active and vigorous participation of a private investigator.

That said, my concern is related less to that first two- to four-year interval than it is to later possibilities, as I've

implied earlier, regarding the possibility of catastrophic failure in even a small number of individuals. So I don't have any major criticism with regard to Panel Question 3.

CHAIR KIRKPATRICK: Thank you.

Dr. Pfeffer?

DR. PFEFFER: If this continued access study were the only information we had, I don't think we would need a statistical analysis to reject this summarily. A 34 percent loss to follow up would not be accepted in any peer review journal in the United States.

That said, I'm not bothered that much by this at all because the detail and quality of the pivotal study was great. And that, to me, stands on its own. So I would cast a blind eye on this data because of the quality and detail of the pivotal study.

CHAIR KIRKPATRICK: Thank you.

Mr. Melkerson, I don't think any of the Panel is enthusiastic about this. But

much like politics, they have to choose the candidate based upon what is realistic as opposed to what would be exactly what they wanted.

And so as such, it is an acceptable issue to relate this data. The feeling was that the pivotal data was good enough that the continuing access would only have changed it if it came up with significant red flags of safety is an interpretation that I would apply. And as such, we think it is okay.

Does that adequate address your concerns?

MR. MELKERSON: Yes, thank you.

CHAIR KIRKPATRICK: Thank you.

What is question four?

MR. PINDER: The applicant compared the surgical complications of the pivotal patients to the first 15 patients of the continued access study to the remaining patients from the access study. In addition, the applicant looked at three investigators

who only participated in the continued access study and concluded that a 15-patient learning curve was apparent.

Please comment on the adequacy of the proposed training program to ensure the sufficient surgeon preparation and knowledge of the surgical procedure.

CHAIR KIRKPATRICK: Thank you.

If the Panel members need to review the training program, it is under Tab ten of our program. It was also -- they had a few slides in their presentation on it as well.

So we will start with Dr. Skinner this time.

DR. SKINNER: Thank you, Dr. Kirkpatrick.

Obviously I think it is clear that if it takes 15 patients to learn how to do this operations, we shouldn't let any of the surgeons do 15 patients. We should have them start with 16.

(Laughter.)

DR. SKINNER: And that would take care of the problem.

Being a little bit more realistic, however, I think we have a situation where we have to balance practicality with the ideal. And I think the training program that is outlined is pretty good. I think that it is about as good as you can do.

Being practical about this, a day-and-a-half of training is a significant amount time out of a surgeon's practice. Hopefully, that surgeon would not perform these until he or she felt quite comfortable with the procedure.

And we have to keep in mind that it is also the hospital medical staff's responsibility to ensure that surgeons performing procedures in that hospital have competence and current training to perform such a procedure.

Based on that, I would have to say that the training program, as outlined by the