in the world.

And since this inaugural event, we treated more than 1,000 aviators, several of whom I've had the chance and opportunity to fly with. If I did not personally believe that Laser Vision Correction was in their best interest, I would not be treating anybody on active duty, let alone an aviator. And I would certainly not be advocating that it be done in civilian communities.

I'd like to thank you for your attention, and the opportunity to present today.

DR. WEISS: Thank you very much, Dr. Tanzer. I should point out, Dr. Tanzer is an invited guest speaker for the FDA, but does not work for the FDA.

Do any members of the panel have any questions? Dr. McLeod.

DR. McLEOD: Dr. Tanzer, a point has been made earlier today that patient selection is key. I'd like to ask you, based

on your understanding of standard of care established in the community for patient selection, would you be able to identify any specific areas that guides the military in being able to obtain the results you demonstrate?

DR. TANZER: We take our patients through an exhaustive preoperative process, including the testing that we provide for them. But they come to us already pre-screened by a cadre of co-managing optometrists out in the fleet in the parent commands that the patients do come from, so right away, they've already been screened at the local level, so to speak, so that they are deemed to be -- as best as possible, they're deemed to be a safe and appropriate Laser Vision Correction candidate before they travel to one of the 20 Laser Vision Correction centers in the DOD.

Once they get there, again, we take them through the standard battery of tests

that we all take all of our patients through in terms of uncorrected and best corrected visual acuity, manifest refraction, cycloplegic refractions, topography, and other imaging devices to make sure that they're an effective candidate for Laser Vision Correction. And then we culminate that in a very extensive informed consent process.

To the extent that we're very honest and up front with these patients, especially our what I call high-value assets, our aviators, divers, special operators, we tell them that if their vision suffers because of this procedure, they could lose that function, they could lose that job.

DR. WEISS: Yes.

DR. McLEOD: Of particular interest would be any particular areas that you might think of, for example, pupil size or so that you may feel the military has a particular position on that may enlighten the civilian population, as it were?

DR. TANZER: You may know, we've published on that. Dr. Schallhorn published in 2003 in the *Journal of Ophthalmology*, and I was a co-author, the report that pupil size cannot be used as a predictive factor of post-operative quality of vision complaints. So, whereas, we do measure pupil size in all of our patients, we don't place any treatment criteria based on that pupil size measurement.

DR. WEISS: Do you have any statistics in terms of what percentage of patients who would like LASIK are screened out by the optometrists, and then of those who come to you, what further percentage are screened out?

DR. TANZER: I don't have a good answer for your first question, in terms of how many are screened out at the local level. But we have an approximate 10 percent rate of when patients do finally come to our DOD centers, they aren't deemed a good LASIK candidate.

DR. WEISS: Thank you. Yes, Paula.

DR. EDRINGTON: What are the conditions for the ones you turn away, why?

DR. WEISS: Dr. Edrington, I just asked Ms. Cofer to ask a question, and then you will follow.

MS. COFER: Yes. I have a question about the glare source you mentioned doing contrast sensitivity testing. Would you please explain to me, when you use a glare source during contract sensitivity testing, does that mean - and this is just to educate me. I don't understand how that's done. Is there a light source that's shined in the patient's eyes during this testing? Is that correct?

DR. TANZER: I didn't mention that we tested contrast sensitivity with a glare source. The study that I mentioned was the night driving simulator study, with and without a glare source. And the source of that glare during that night driving simulator

study was a light that simulated the glare from headlights in a rearview mirror.

MS. COFER: And you're aware that when a patient is facing an oncoming headlight that their pupils constrict, and that blocks out the spherical aberrations in the periphery of the cornea. Is that correct?

DR. TANZER: That would be physiologically correct, yes.

MS. COFER: Thank you.

DR. WEISS: Dr. Edrington.

DR. EDRINGTON: I just wanted to ask about the 10 percent, when they come to have the surgery that you do not perform the surgery. What are the reasons?

DR. TANZER: Well, the reasons are the standard reasons that we published, whether it has to do with cornea physiology, irregular topographies, the corneas being too thin for a safe procedure, refractive instability. Those would be four reasons right off the bat that would make the patient

perhaps not the best suitable candidate for Laser Vision Correction.

DR. WEISS: Any other questions from the panel? Seeing no other questions, thank you very much.

DR. TANZER: Thank you.

DR. WEISS: We will now proceed to discuss the panel questions from the FDA that are before us. Dr. Lepri will project the first question. Momentarily.

While we're waiting for it to be projected, I can also read it out. The first question is, "Please discuss any recommendations you may have for modifications to patient labeling of excimer lasers for LASIK." So the question that I'd like the panel to think about and contribute to at this point is modifications for patient labeling of excimer lasers for LASIK.

Perhaps we can go just around the table, and I'll call on you. And if you have any comments, please contribute them. If you

don't, you can pass.

Dr. McLeod, do you have any suggestions, or any thoughts from this discussion on what could be done to clarify or improve the patient labeling of excimer lasers?

DR. McLEOD: Well, I think this may be a difficult issue until we have better data. But somehow, when we're able to quantify or better express the issues that psychological state and reasons for having surgery come into play, perhaps some mention should be made for patient consideration of the potential for issues for people with a background, if, indeed, we do generate data that can support that.

DR. WEISS: Thank you. Dr. Musch.

DR. MUSCH: To follow-up on Dr. McLeod's comment, labeling often reflects what we know, and doesn't reflect what we don't know. And I think there are many aspects of risk related to LASIK that we have yet to find

out. And I don't know if it's appropriate to put in labeling, but it would be nice to have a caveat statement about some risks yet to be uncovered.

DR. WEISS: Dr. Heuer.

DR. HEUER: I'm not sure if this is under labeling or under the website, but on the website, the graph for dry eye seems to suggest that by four weeks that's gone.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: What we tried to convey during our presentation is that this is data that represents data collected as part of a pre-market assessment for the LASIK devices, i.e., it's data from safety -- cumulative data from the labeling of all the LASIK devices. And it is intended to present the general patient, not the extremes of the population, the average outcomes.

DR. WEISS: And I would ask if perhaps we can hold that discussion to the next question. Do you have any comments

on the labeling?

DR. HEUER: I'll pass on the labeling.

DR. WEISS: Okay. Dr. Edrington. Dr. Huang.

DR. HUANG: I do have a couple of recommendation. As we know, dry eye is a significant side effect of the LASIK surgery, and I think patient labeling should emphasize many aspects of the dry inducing events. And, certainly, we have talk about autoimmune diseases and various cornea pathology, but I think there's one item is missing, is the hormonal replacement therapy. Even though there are some indication talking about hormone fluctuation can affect surgical outcome; however, there was no specific indication, especially for the female population, and so I think hormonal replacement therapy probably should be included in the patient labeling.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Two comments. First, to Dr. Huang's comment. The first contraindication that's in your attachment states, "If you have any of the following situations or conditions you should not have LASIK, because the risk is greater than the benefit." And the first bullet is, "You are pregnant or nursing, because these conditions may cause temporary and unpredictable changes in your cornea and the LASIK treatment may importantly change the shape of your cornea."

DR. HUANG: But I'm talking about a menopausal woman.

DR. EYDELMAN: Okay. I'll come back to that, but I also wanted to address something Dr. McLeod stated earlier. The precautions start out by saying, "It is unknown whether LASIK is safe and effective for the following conditions." So we actually provide a long list of things that we say we don't have enough data for, so I don't know if that is what you were trying to address.

DR. WEISS: So I think in terms of that, Steve, we could potentially have some place to put something about psychologic issues, so that at least it would be included, even if we don't have the information. Yes?

DR. McLEOD: Just one follow-up on the issue of collagen vascular disease. Perhaps there really should be some revision of that section that distinguishes between collagen vascular disease associated with dry eye, and other collagen vascular diseases, since the most current data really do seem to suggest that non-dry eye associated collagen vascular disease is not necessarily associated with difficulty with LASIK.

DR. WEISS: Dr. Huang, did you have any other comments?

DR. HUANG: Yes. The other comment is regarding the patient labeling. Most of the patient labeling did not really specifically indicate that there are perspective excimer laser to be used for their

correction, so I think maybe we can -- maybe it's in the physician labeling. It is on some of the patient labeling information that I have, that it did not specifically clarify to the patient what type of laser correction can be used.

DR. EYDELMAN: No, actually --

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: I'm sorry. I believe every one of our patient labeling states the indication, and the refractive indication for which that device is approved is part of the indication.

DR. HUANG: Perhaps, maybe some of the prevailing patient information is outdated, because there are several updates of the software version. And then most of the patient information provided by the excimer companies usually just initial approval indications.

DR. EYDELMAN: Dr. Eydelman, again. Software updates will not affect indication.

If any change of an indication requires a submission and a separate approval from the FDA, and to that extent they -- all the labeling would be modified to reflect that.

DR. WEISS: Dr. McLeod.

DR. McLEOD: Just one other point on keratoconus. It probably would be worthwhile to specifically identify a risk associated with a family history of keratoconus, or at least to prompt further in-depth screening.

DR. WEISS: I think, also, we should probably be adding "and other ectatic disorders", if it's not listed, such as pellucid.

One thing that I was wondering for many of these questions that patients can view the data, is if we could have a schematic of what the symptom we're describing is, in addition to just using the words. So we saw some slides here of what a starburst looks like, what the HALO's look like, what 20/25

vision, which is very, very poor, 20/25 vision looks like. I don't know if this is possible in patient labeling, or maybe it would only be possible on the website, but to have some -- give a patient some diagrammatic idea of what the words actually translate to in terms of what they'd be looking at. Dr. Smith.

DR. SMITH: I don't have anything for the patient labeling.

DR. WEISS: Ms. Cofer.

MS. COFER: I believe, based on the latest scientific data, and I probably should just, just for background information, when LASIK was approved originally many years ago, we didn't know a lot of the things that we do know now. There have been thousands of scientific studies about LASIK since its approval by the FDA, and so there's a lot of new information out there that's not incorporated into the labeling. So I actually have what you would call a laundry list of things that I think would be appropriate in

the labeling, if I could go through those.

DR. WEISS: That's fine.

MS. COFER: We now know that future cataract surgery is complicated by having had corneal refractive surgery. And I believe that's an issue that patients are not being informed of before they go into LASIK, or any form of corneal refractive surgery. We'll all face cataracts sooner or later if we live long enough, and I think that's something that patients would like to know, that when they reach the age that their natural lens becomes cloudy and they need cataract surgery, that they are going to have problems with their cataract surgery because they've had LASIK. And I believe that would be something that should be in the labeling.

Do you want me just to continue?

DR. WEISS: Yes. I'm listening, but I want to make sure we get everything down.

MS. COFER: Okay.

DR. WEISS: So, yes, please continue.

MS. COFER: It's also clear now that the change in the cornea after LASIK or other corneal refractive surgeries causes a problem with intraocular pressure measurements, and that's something that patients are not aware of. I don't even know if most eye doctors or optometrists are aware of it. Maybe they are, but it's certainly something that could become a problem for patients, especially a patient that is beginning to develop ocular hypertension, and possibly glaucoma. And patients do not know that they need particular attention paid to their optic nerve, and any signs of ocular hypertension, so that should be in the labeling.

And something that is fairly new in the literature coming out of the Mayo Clinic, is these reports of persistent decrease in corneal keratocyte density. I know the long-

term implications of that on the health of the cornea seem to be unknown. Maybe that should be listed as a labeling warning, that we do see this long-term persistent increase in corneal keratocyte deaths, and we don't know what that will do to the health of the cornea, and the function of the cornea long-term.

I don't think patients are being informed that the LASIK flap heals only very minimally. I believe the research out of Emory showed that the flap itself heals to only 2 percent of the original tensile strength of normal cornea. There is a scar at the margin that heals stronger, about 28 percent, but if that scar is broken through trauma or surgical relift of the flap, the LASIK flap easily lifts. It can be easily lifted, many years or forever. And I think patients are told that the LASIK flap heals, they go on with their life. They're not warned to wear protective eye wear, and I think that's something that patients should

know, that the flap heals only minimally after LASIK.

Also, we know now, based on literature, that creation of a corneal flap and ablation of tissue into the anterior portion of the cornea leaves the cornea much, much weaker. And I'm talking about the biomechanical strength of the cornea is much weaker after LASIK than prior to LASIK. The cornea has to withstand the intraocular pressure of the eye, and this weakened state of the cornea, which is a permanent state. It doesn't recover biomechanical strength. This permanent weakened state of the cornea could pose problems for patients.

We've seen many, many case reports of late onset ectasia occurring many months or several years after seemingly successful LASIK, and I believe patients should be warned of that.

I think it's also unclear that surgical correction of myopia will take away a

patient's ability to see up close after the age of 40 simply by removing their glasses. I can talk from my personal experience. I was told you'll need reading glasses after the age of 40, whether you have LASIK or not. I now know that I would not have needed reading glasses after the age of 40. I could have kept my myopia and just removed my glasses, and I would have been able to see up close. And I think that's misleading to tell patients that they'll need reading glasses whether they have LASIK or not. If they're myopic, if they're nearsighted, they can remove their glasses and see up close, and I think that needs to be in the labeling.

I think the labeling should warn patients about - and maybe it does now, I'm not sure - about bilateral simultaneous LASIK being a risk for vision loss in both eyes.

DR. WEISS: I believe that's in there already. I wonder, since you have a long laundry list, perhaps you could read the

list. If you could maybe read the individual items, and then if we need clarification, I could ask you.

MS. COFER: The next one is that I'm asking that there's something in the labeling that communicates to patients that loss of visual quality after LASIK is frequent. It's not a rare event. It's a common event. And I don't think patients are expecting to loss visual quality after LASIK, but that's what happens. And that's been shown in clinical trials, including Wavefront LASIK, is that there is a loss of visual quality, which can be measured by wavefront aberrometry.

DR. WEISS: That I might disagree with you on, because I think then we're getting into statistics. And then the question is, how detailed do we want to be in the patient labeling? And we may want to be more detailed. However, the question is, do we want to then list every single aspect? If

we speak to the presentation by Dr. Tanzer, it appeared that it was overwhelming these people were happy with the visual quality. So then it gets somewhat open to discussion. And we can open it up to the panel in terms of how detailed does the patient labeling become.

We had heard a criticism in the public session that already this is too difficult for the average patient, and so it may, if they even get it, get tossed aside. We do want something that people will read and see if they have the opportunity to. And part of the discussion here today will be how best to give patients the opportunity to see this data.

Does any other members of the panel have any comments on that? Do you think these -- what should be the statement about patient visual quality? Is it sufficient what is presently in the patient labeling, that halos, et cetera, may be experienced. What are other people's thoughts? Dr. Huang, and then Dr.

McLeod.

DR. HUANG: I second the Chairman's recommendation.

DR. McLEOD: At this point, I would agree. When Ms. Cofer gets to the end of her list, I probably want to bring up some questions about some of those issues.

DR. WEISS: Okay. Why don't we keep on going?

MS. COFER: Okay. I'd like to see symptoms, such as dry eyes and night vision impairment moved from the table called "Symptoms", to the table called "Adverse Events and Complications", because I don't -- we heard a lot of testimony here today about dry eyes and night vision impairment. And these are complications, they're clearly complications, and I don't think -- I think it's deceptive to put those in a separate category, and call them "symptoms", and downplay those. They're very serious life-altering issues.

DR. WEISS: I'm going to defer to Dr. Eydelman, because much of this has to do with the way these studies were originally put together for the PMAs, and consistency among how the FDA looks at these things for all devices. Dr. Eydelman.

DR. EYDELMAN: Actually, I believe that all of the pros, and you all know what that means, are usually reported in labeling under "Adverse Events and Complications", a compiled section that would address both objective and subjective outcomes. So the dry eyes would be in that section already.

MS. COFER: I don't recall seeing the night vision impairment under the "Adverse Events". It's always been under a table called "Symptoms".

DR. EYDELMAN: We'll take your note into consideration.

MS. COFER: I believe it's the MEL 80, the most recent approval of LASIK. I'm using that one as a sample for my next

request, which is that pupil size be listed actually a contraindication for pupil size over -- that's larger than the optical zone of the LASIK. And I do believe that's in one of the most recent approvals. And I would like to see that on all lasers, because anyone that has LASIK with an optical zone that's smaller than their scotopic pupil size is going to see these night vision disturbances.

DR. WEISS: Okay. I think we've just heard testimony, and I think Dr. Schallhorn had done that study, and Dr. Tanzer participated, that there was no evidence for that. We may want to go back to Dr. Schallhorn, but do any other members of the panel want to comment on this? Dr. McLeod.

DR. McLEOD: So this is specifically on the pupil size issue?

DR. WEISS: Yes. Should you warn the patient that if, let's say, the ablation zone is less than their pupil, they should not have this procedure performed?

DR. McLEOD: Yes. One of the reasons that I'd asked Dr. Tanzer the question, is that many of us in the community are familiar with the original study that was published. However, publishing the study does not, necessarily, correlate with actual practice. If, indeed, the practice is as described, certainly, that would be consistent with the literature that's established that does not, at this point, strongly link the two. So I think that it would be -- it's a very difficult area, and I don't think that the patients' interests would be well-served by an inaccurate description of the situation.

DR. WEISS: Dr. Smith.

DR. SMITH: I would agree with Dr. McLeod's comments. And, also, you're really getting into more complicated issues related to that specific patient if you say a specific pupil size and a specific laser. There are a variety of factors that are considered by refractive surgeons in individual patient

assessments, and while providing as much information to patients as possible is important, I think overwhelming patients with a lot of information that may be difficult to interpret, putting it in the contraindication section, specifically, isn't warranted at this time.

DR. WEISS: Ms. Niksch.

MS. NIKSCH: Yes. I would also agree with the comments from Dr. McLeod. And, again, every sponsor brings forward data from their clinical trial to FDA. The last part of the approval process is a significant negotiation process, and detailed review of all of the claims, and all of the contraindications, and all of that detailed information specific to that particular device, so, in general, on this particular one, but in general on many of these comments, unless they can be specifically related to the specific device in question, industry would be opposed to making these sort of blanket

changes to all of the patient labeling.

DR. WEISS: We are going to need to proceed to the other questions, so I understand that you have a long list. I would like to give you the opportunity, if you could just read off the list, because I do want to give Mr. Bunner an opportunity to comment, and Ms. Niksch, and then go on to the second question.

MS. COFER: Depression is commonly seen in LASIK patients with dry eyes and/or night vision disturbances. Depression and suicidal ideation must be studied by unbiased mental health practitioners, including in the warning in the device labeling.

Recommended labeling changes cannot wait until FDA has the results of a future study of patient quality of life. FDA must take action now to protect the public health. Perhaps there should be a device recall until proper study of complications, both short and long-term, permanent pathologic changes to the

cornea, quality of life, and depression is completed.

DR. WEISS: Thank you. Mr. Bunner.

MR. BUNNER: Nothing.

DR. WEISS: Thank you. Ms. Niksch.

MS. NIKSCH: Just a comment on the last comment. I'm certainly opposed to any sort of drastic action, such as any recall, or discontinuation of any LASIK products based on the anecdotal information. I think we are looking forward to results from the prospective quality of life study, and at that time, would be appropriate to reconvene, and determine what appropriate changes might be required to physician and patient labeling.

DR. WEISS: Dr. Huang.

DR. HUANG: Perhaps I recommend FDA to consider post-consultation evaluation of the patient's mental status, or the patient's comprehension of the consultation. Oftentimes that after the patient come to my clinic, and for various consultation, I ask them to repeat

what I told them, or I ask them repeat the questions in their own words to see that they're really representing what I told them. So, as a result, I think that communication between the physician and the patient, and then also the patient's expectation will be more realistic.

DR. WEISS: Dr. McLeod.

DR. McLEOD: I just wanted to take this opportunity to briefly touch on a couple of issues that Ms. Cofer may have raised, particularly with regards to flap and corneal strength.

In terms of the labeling, I think that it's -- I certainly think that it does -- it is important to point out that there is variability in the healing of the flap. I think a categorical statement that all corneas are necessarily vulnerable to -- any particular quantifiable degree of traumas is problematic, in that clearly, first of all, there are no good studies beyond the best data

that we have, which does come from the military on flap healing after surgery. And, indeed, the data are limited.

Certainly, in practice, it's widely recognized that there's tremendous variability in flap healing after surgery, so that in some cases, even relatively soon after surgery, there can be tremendous difficulty, even microscopically surgically lifting a flap; whereas, in other cases, there really can be relatively easy flap dislocation. So I think that a statement that recognizes variability, but does not suggest that it is inevitable that there is a decrease in flap strength is important to clarify.

The second issue is related, which has to do with the claim or the suggestion that there is a pathological, or clinically significant -- in other words, if this is going to enter into patient labeling, then one would presume that this is something that would be of significance to the patient. And,

certainly, there are no good studies, again, looking at the absolute change in biomechanical stability and strength of the cornea.

Certainly, there's very strong evidence that in specific cases, that there is pathologic change in biomechanical stability, specifically in those cases that are at risk for keratectasia. On the other hand, given the fact that the vast majority of corneas do show topographic stability over time, it would suggest that any statement of significant change in the stability and strength of the cornea really should be categorically stated.

DR. WEISS: Dr. Musch.

DR. MUSCH: Perhaps I'm the only one who is naive here, but I view all of these suggestions as worthy of follow-up and investigation, but not, necessarily, being endorsed by us as a panel. When I hear, for instance, that keratocyte loss is observed around the periphery of the flap from a single

study at Mayo, I'm not sure that qualifies as labeling requirement.

DR. WEISS: So in addressing the first question that was posed to the panel as far as recommendation of labeling, it appears that the ones that - and I'm going to, I guess, use Chair's prerogative to pull some of these out - the ones that most of us can agree on, and after I make this statement, if there is disagreement, please address it, and these are to the panel members - to indicate that cataract post-operatively, we know that there are some issues in terms of checking the intraocular pressure. If anyone disagrees with that, including that, can you just sort of raise your hand? So we should include something like that, I think the panel agrees.

The issues in terms of figuring out the implant measurement for cataract surgery if you've had LASIK, and everyone is in agreement with that one. If you can do, or include a couple of pictures of what a halo

would look like, a starburst, to indicate what the visual symptoms are.

If we do not have a strongly worded sufficiently, and we may already, to indicate for those people who have keratoconus, other ectatic disorders, pellucid marginal degeneration, we may want to mention that. Now that that's become very well known, we may want to mention that by name, where it was not mentioned originally.

And, also, we should -- someone who has a strong history of keratoconus should be, perhaps, examined more carefully, or words such as that.

Another suggestion was made to distinguish those patients who have collagen vascular disease in terms of being poor candidates, versus those who have collagen vascular disease with dry eyes, who would be particularly the ones we are concerned about.

One mention was made of - and this would be one of the perhaps softer, and the

FDA would have to determine how this would get put into this - but in terms of the psychologic issues, either before, or for those patients who, perhaps, had no psychologic issues that were manifest before, or diagnosed before, but when dealing with the adversity of a poor visual outcome, then manifested psychologic issues. And I don't know how one would put that in there, but that may be something to be addressed.

The issue with dry eyes, I know that we have that in there, the fact that hormonal replacement therapy could adversely affect this in some patients. I don't know how detailed you want to get in terms of this.

And I think that basically summarizes most of what was said here, that we could reach agreement on.

We will then go to question number two.

DR. LEPRI: "Please discuss any recommendations you may have for modifications

to FDA's LASIK website."

DR. WEISS: Why don't we start on the other end of the table.

MS. NIKSCH: Barbara Niksch. The only comment that I would have is really, there seems to be some inconsistencies with the professional societies web pages with regard to just the technology, in general. So I would encourage the Agency to work closely with the professional societies to insure the information is consistent. That's really it.

Actually, I also just want to comment. I think that actually the information regarding if a patient would be an appropriate candidate or not an appropriate candidate seems very thorough. However, based on some of the discussions today, I can see some areas where we might want to add some additional information. But, in general, I think it's very thorough, at this time, regarding a lot of the issues that were brought up from patients that spoke earlier.

DR. WEISS: Mr. Bunner.

MR. BUNNER: Yes. Richard Bunner. I have a couple of comments. One, I guess is just a general observation, and I think in some ways, on the website, is the comment directing to determine whether or not they're a risk-taker. And I guess I just -- I wrestle with that as a concept, because culturally, I think for some folks it might be considered more of a challenge than a warning. And I'm not sure that it is a sufficient warning to me as a consumer, as to what that really means. Because of all the other contraindications presented, it might even be worth not having there, or having it rephrased. I kept stumbling over that on the website.

In looking at that issue of risk, I'm not blessed with having high-speed internet access. I'm out in a rural area where I have dial-up, so going onto the website, wanting more information related to risk, I end up referencing one of the laser

sites. Well, the download time was so incredible that I finally stopped, so you may even - just as a point of information - direct the users to what they may experience with the website with their access to the internet.

But in saying that, what I was trying to look for was some of the information presented this morning as to well, how often, as a consumer, could I expect that I might find a contraindication, or a negative outcome? And I didn't see that very clearly presented on the website. Now, maybe it's there, but I didn't get to it quickly, and I was trying to find that.

And then the third comment I had is that I did go to both the LASIK website, and I went to the intraocular lens website, and there are some inconsistencies between the format of the two sites. It might be useful to have a bit more similar.

What I was mostly drawn to, which I thought was helpful, in particular, was on the

intraocular lens website, was questions for your doctor. That was not one of the key buttons on the LASIK site, and I think that's a useful key. And it would be a good one for the LASIK site. And that concludes my comments.

DR. WEISS: Ms. Cofer.

MS. COFER: I don't have a laundry list this time. Sorry to disappoint everyone. I would just like to see something on the website pertaining to surgical correction of myopia. And, again, the issue that patients would retain the ability to see up close by not having your myopia surgically corrected.

DR. WEISS: Dr. Smith.

DR. SMITH: It's listed several places on the website, the issue of re-treatment. It's kind of scattered throughout. You might consider maybe a separate section on that, just in terms of making clear expectations regarding that, a little bit more information in a separate section, perhaps.

DR. WEISS: I would suggest photos also be placed on the website sort of similar to those that the patients have described at this meeting, as far as what they actually see.

I would also think it would be helpful if there were some easy link to patient labeling, because to get to the individual PMA, and then the doctor labeling, and the patient labeling is somewhat difficult.

The other part about the risk taker, what's been underscored here, which is something similar to what I tell my patients, is that even if the risk is .5 percent, or .05 percent, if it happens to you, it's 100 percent. And sometimes some of my patients don't want to think about what happens if the risk happens to me. And, certainly, in my laser practices, it's also under -- it's not underscored, and it's not emphasized. But if there was some way, as was mentioned, to

convey that slightly stronger, is that if you cannot -- if you would not be willing to have an adverse event happen, and, of course, no one wants to. No one wants the adverse event; however, if you could not tolerate an adverse event, you should not have LASIK.

And that will get back to one of the last public speakers commented that there were many people on this panel that wear glasses, so how can we do refractive surgery and wear glasses? And the reason, for me, is two-fold. One is, I like my up-close vision, and so when patients come in to me as a refractive surgeon of a certain age, which I will not mention, I emphasize that as an eye surgeon, I can read without my glasses, and I love that. And I can operate without my glasses, and I love that, so while LASIK works and it's good, it's not for everyone. And so that if you tell me that as a myope you're sitting at your desk most of the time, and you don't need glasses, and you only want the

LASIK for when you're golfing, I'll tell you as a patient you probably don't want the LASIK, because most of the time now you're going without glasses. So that's one aspect.

The second aspect is, I would not tolerate any risk for myself, and I know myself. And does that mean LASIK is good or not good? It means LASIK is good, but not for everyone. And the key thing that has also been emphasized at this meeting, it's key to get the proper information, and be screened properly, and understand what you're looking for, and what this procedure can do, and not have a moratorium on the procedure, I think. And perhaps I'm speaking out of turn as chair, but I'm speaking maybe as an individual, and then I'll go back to my chair mode; is that, I think we need better screening, better information, better -- in some cases, perhaps some better doctors for some of what was experienced here, but not to throw out the baby with the bath water. It's not that the

device is bad, it's that, for example, if you were not told that if you took off your glasses before surgery, you wouldn't be able to have the same ability to read after surgery. That's lack of information, not a bad procedure.

Dr. Huang.

DR. HUANG: My comment is specifically related to the user friendliness of the website. To me, this is a refractive surgery, in general, so that I think maybe FDA can put either the IOL refractive -- the LASIK, and maybe PRK, and all those therapeutic modalities, so the patient, when they come to consider such a procedure, they have a quick reference, rather than going through different therapeutic modalities to look for the information they are looking for.

DR. WEISS: Dr. Edrington.

DR. EDRINGTON: I wear glasses because I see double without them on. One of the things I think would be helpful, just as a

consumer, we're -- there's a lot of fine print out there. So if you're signing a new mortgage on your house, it takes you hours to sign your name, and you don't have time, actually, just to read everything there. I've been guilty of that recently.

I think it would be helpful when the fine prints there are saying there's a complication, or a symptom such as dry eye, that maybe the incidence of percentage of patients that have that as a side effect, that would be helpful for me, as a consumer, to know that's a high risk, and I'm willing to take it, or that seldom happens, and I'm willing to take that small risk.

On the page one of four for "What should I expect before, during, and after surgery"? Since I'm involved in the contact lens field, having this little formula, a bar chart telling me when a contact lens should be removed, or how long it needs to be removed before LASIK should be performed, that seems

to miss the boat, to me. I understand that's very common, but the issue is stability. And this is a nice guideline, but, hopefully, every LASIK surgeon is looking for stable refractions, and stable corneal measurements, as opposed to some sort of time line.

And I think that needs to be emphasized not only to the surgeons, but also emphasized to the public, because sometimes they get upset when you've gone after the two weeks, and they're not stable. They think it's your fault, somehow.

I agree with Ms. Cofer about the — this is on LASIK Surgery Checklist, page one. I agree with Ms. Cofer on the fact that if you are nearsighted, some patients just don't understand that they won't be able to see up close after the procedure. They'll sit there and tell you no, I see fine up close. I'm going to have this done to take care of my distance vision. I see just fine up close. Well, they won't after the procedure, so I

think needs to be clarified strongly to every patient.

Also, this says, "May still need reading glasses." I guess that could happen, but almost everybody at some point will need reading glasses, either early after surgery, forever after surgery, or maybe after 10 years after surgery.

Also, on the LASIK checklist, it says "Know when to seek help." I think it would helpful to have something there telling the patients what those risks might be, not so much when they're asking about the refractive surgery, but some patients might actually go this website if they're having complications to see whether they need additional help. So I don't know if there should be another session that would maybe show them what a red eye looks like, or here are the things that you need to immediately call your eye care practitioner or your surgeon if you notice any of these. It might be more helpful after the

procedure, as opposed to at the time of the procedure.

And the other thing I'd strongly like to agree with Dr. Weiss on, which is, the device is not bad. I don't think we're, in a sense, judging the device here. I think the device is fine.

DR. WEISS: Dr. Heuer.

DR. HEUER: I think a lot of patients that have dry eyes don't realize they have dry eyes. And I think what would be helpful under precautions, and maybe in the checklist would be a link to a dry eye self-survey. I think the do's or something like that, that patients could see, do a -- say, I have this problem. Maybe I ought to think twice about it.

And in that same vein, we started this conversation inappropriately in the last question, but I think while -- under "What to Expect Under Surgery", where the dry eye box ends at four weeks, is that the average, is

that the 95th confidence level, 99th percent confidence level? Having the box end, I think is very deceptive to the patient, because they say this is a short-term thing, even though it says other ways, that it may not end. I think having that picture, many people learn a lot more from a picture than they will from all the verbiage.

DR. WEISS: Dr. Musch.

DR. MUSCH: Well, since it's true confessions time, I've worn glasses since I was in first grade. I'm a pretty happy camper with them, and the degree of myopia I have exceeds that which most of the LASIK would take care of.

When I read this website, I think back to writing an informed consent, and having a high school student look at it and see if they comprehend it. And it's always good to revisit something like this. There's a lot of text in here, and you might -- I'm sure if you ran a text check on it, it would

read at more than a high school level in many parts of it, so it would be worthy to revisit that for readability.

And I don't see a comment in there under the "When is LASIK not for me", that would impact on a person like me, with a spherical equivalent in the minus 11-12 range. That seems to be a time when you'd start to think LASIK might not be good for you.

DR. WEISS: Dr. McLeod.

DR. McLEOD: First of all, I'd like to endorse Dr. Heuer's idea of the self-test for dry eye. I think that's an outstanding idea, particularly given that that is, indeed, one of the most common things that we have to put up with.

I think that, first of all, just to start with, the "When is LASIK not for me", page, the general organization of this page, "When is LASIK not for me" really doesn't seem to flow very well. It doesn't make a lot of sense to me.

What happens, it's divided into these different categories. You're probably not a good candidate if, and then it goes to precautions, but the things -- the elements within each of those categories seem to overlap to some extent. There are lifestyle things in one, and then there's specific medical conditions. And then you've got the same thing in another section.

And under "Precautions", the statement is, "Safety and effectiveness has not been determined in patients with some diseases." Keratoconus is listed under there, and I think it's a consensus opinion that keratoconus is well-known not to be acceptable for LASIK surgery.

Just a couple of points of clarification. There's a point under "Probably Not A Good Candidate", that specifies that corticosteroids may prevent proper healing after refractive procedures. That's one example of a place where going over

the document that -- with a specific eye to identifying what current consensus opinion is, is probably worthwhile, since corticosteroids, I think is well known, are actually considered part of standard of care as treatment, following treatment.

On the next page, specifically under the area of "Large Pupils", again, I would recommend that the FDA revisit the current literature, and make a conscious decision about what the FDA wishes to do with that particular statement. That's on page 2 of 2.

Moving forward, just a minor point. There is under the section "What are the risks? How can I find the right doctor for me? During surgery, malfunction of the device, such as cutting a flap of cornea through and through, instead of making a hinge may lead to irreversible damage to the eye." That's probably not a good example. There are certainly better examples of things that can

happen to the microkeratome. That actually would not be considered one of them from a technical point of view.

Finally, under the LASIK surgery checklist, again, I already raised the point of the distinctions that should be made with autoimmune disease. Medications also list steroids, there's a pupil size reference there, and on the last page, there's the statement, "Be prepared to wear an eye shield", a minor point, but that should be specified that it's during sleep.

The biggest issue really is, though, I think that the overall organization, particularly of the section, "When is LASIK not for me"? I don't think is really helpful in patients really understanding what are true contraindications, and how to categorize the truly significant issues, and then through other things that may be less significant. Weighting it so that people understand the important issues, is really, I think, key.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: I just wanted to add one comment. We now heard from a couple of panel members recommending that we add a link to a dry eye questionnaire. I wanted to point out that as of current time, the only validation that has been performed on that, or any other vision-related questionnaire, has been for pen and pencil administration. So the study that is currently undergoing, and is supported by NEI and FDA, is aimed exactly at that, in trying to validate web administration of previously validated questionnaires in pen and pencil. So if that study proves that the web administration is, indeed, equivalent, then this would be one way that we can then incorporate these kind of questionnaires on the web, and include links on our website.

DR. WEISS: Yes.

DR. MUSCH: I wasn't going to comment on that, but having brought that particular study up, I noted that you were

taking pieces from existing validated questionnaires, putting them together, and then testing to see if web administration differs from written, or doing it on paper. And, so, you have then gone beyond the validation status of each instrument, and come up with a unique combined instrument. Am I mistaken on that?

DR. WEISS: Dr. Smith.

DR. SMITH: You're referring to the NEI/FDA study. Correct?

DR. MUSCH: Yes. Wherein, you take five OSDI questions, one NEI VFQ question.

DR. SMITH: So none of the questions were taken separately. They are domains that were taken, full domains that were separately validated, so we have validation data on those domains. We would love to have as much information as possible. However, as you know, many of these instruments are quite long, 42 items, 25 items, the OSDI is probably one of the

shortest.

In order to try to get information related to dry eye, satisfaction, quality of life, the goal was to try to get units that were validated in and of themselves as domains or sub-scales, the driving sub-scale from the NEI VFQ, for example. These were the suggestions that were made from our psychometricians that reviewed the study design.

We certainly would love to have more data, but practically speaking, if you're trying to make this a study that people can do quickly on the web, that can actually be done in refractive surgeon's busy offices, when you're not going to get fatigue factor towards the end of the 50^{th} question, we had to balance all of those concerns.

Certainly, if there are specific domains that you think would be better, I'd love to hear your thoughts on that.

DR. WEISS: I think we're going to

move on, and just summarize the answers that we've obtained on this question. And this relates, question number two, to the website. The recommendations from the panel were to give a little bit more information for the patient on what is meant by if you're not a risk-taker, you would not want to have this procedure. Some more clarification of that. Add photos of what the visual disabilities actually mean, have statistics for the frequency of some of the adverse events, side effects, or complications, have a link for a patient who wanted to get the patient labeling, let's say, for that particular laser to read in more detail, underscore the fact that if you have LASIK and get excellent distance vision, you will need reading glasses when you get to mid-age, or if you are mid-age and already have excellent reading vision, you will lose that if you are presbyopic, and get your distance vision, instead. Have a separate area concerning re-treatment, and the

stability for -- indicate for contact lens removal, it is not just the duration that the contact lens is removed, it is that refractive stability has to be reached.

I'm not sure if we concluded to have a link to a dry eye website or not at this end of this. If there's a valid instrument, we can link it. If there's not, we would not. There were a list of advice by Dr. McLeod for the, "When is LASIK not for me" portion of the website, as far as rewriting that in a, I guess, more coherent fashion, revising the mention of steroid, because this is used often post-operatively, revising the question about the pupils to correspond to what is now known, putting something in about a distinction with autoimmune disease versus autoimmune disease with dry eyes, having a better example with potential problems that can occur with a microkeratome.

Dr. Huang has been scribing for me, so I'm going to ask you - there have been

three that I left out, update improvement from any of the manufacturers that maybe were not included in the website, improve the download speed. That may be the hardest thing to do. And simplify the language.

We will now move on to question number three. Yes, Mr. Bunner.

MR. BUNNER: Practical question. Richard Bunner. About the button similiarities between the intraocular website, and the --

DR. WEISS: Yes, make it --

MR. BUNNER: Well, the one button was "Questions for your doctor." I thought that was a very useful one on the intraocular site, have that on the LASIK site, because I don't believe it's there. And that was my recommendation.

DR. WEISS: Okay. Thank you.

Question number three.

DR. LEPRI: "FDA is currently evaluating the ANSI Z80.11 Laser Systems for

Corneal Reshaping Standard for recognition. Please discuss whether you recommend that the FDA recognize the standard in its entirety, in part, or with specific additions."

DR. WEISS: In interest of time, for the next two questions, I'm just going to ask for contributions to those of you who have specific changes that you'd like to see made, as opposed to calling on every individual.

Does anyone have any suggestions for changes to the ANSI? Yes, Ms. Cofer.

MS. COFER: Now, I just want to be clear we're all looking at the same thing. Is this the -- what is it, three pages in our binder, or four pages in our binder. Is that what we're referring to?

DR. WEISS: Yes. I think we're referring to number eight in your binder.

MS. COFER: Okay. I think someone might have touched on this already, but I just wanted to be clear on that. In the ANSI Standards, will there be a clear definition of

mesopic? In other words, there are differences between scotopic, low-mesopic, and high-mesopic vision, and pupil size can fluctuate dramatically between high-mesopic and scotopic, so will that be clarified in the ANSI Standards?

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Yes, that is in there. And if I can just address something that was stated earlier. We cannot -- we're not in charge of the ANSI Standard. I just want to make it clear. We're not discussing modification to the standard. What we're discussing is FDA's recognition of that standard, and that can be done in its entirety, in part, or with specific additions. But the standard exists, and it belongs to ANSI.

DR. WEISS: Thank you for clarifying that. So with that, I guess, better explanation, is there anything -- maybe I could start with. Is there anything that

anyone objects to in the standard that was mentioned. Is there anything that anyone would feel not comfortable with? Yes, Ms. Niksch.

MS. NIKSCH: The understanding is that the standard was intended for devices affecting sphere and cylinder only, was not intended to consider high order operations. Is that a correct understanding?

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: It does astigmatic. It was originally written for conventional treatment, but it does not -- I would have to check the scope, as it was currently written. Perhaps I can ask Dr. Hilmantel to step up. He has an official copy of the standard, so we can read the actual scope. Perhaps you want to go on, and we'll come back to that.

DR. HILMANTEL: The standard applies to any laser system whose primary intended use is to alter the shape of the cornea through the removal of corneal tissue

resulting in the improvement of visual performance. This standard addresses a vocabulary of performance", that's all it says.

DR. WEISS: So what's the answer to the question?

DR. HILMANTEL: The answer is it includes all lasers, it includes both wavefront lasers and conventional lasers.

DR. WEISS: Yes, Dr. Eydelman.

DR. EYDELMAN: But it does not provide the distinction that you particularly were seeking.

DR. WEISS: Dr. Edrington.

DR. EDRINGTON: I see that on page three that was in our group here under "Evaluating Safety", that there's nothing on topography or wavefront. Is that what we're referring to? Can you make suggestions?

DR. EYDELMAN: So you're suggesting -- Dr. Eydelman. So you're suggesting to include topography evaluation for --

DR. EDRINGTON: Wavefront, topography, something that looks at corneal -- I mean, looks at the surface regularity, or some indici for surface irregularity.

DR. EYDELMAN: Okay.

DR. WEISS: So from what I'm hearing from the panel, the fact that this includes all lasers, but does not distinguish between conventional and wavefront, there should be something added in here to talk about performing wavefront measurements, or topography. Is that correct?

DR. EDRINGTON: Well, even if it was just regular LASIK, I still think you -- if you had an adverse event, not an adverse event, but if you had change in topography of some measurable amount, and that that would be indicated to you, regardless of whether it's wavefront or not.

DR. EYDELMAN: I believe the standard does address that. Perhaps, Dr. Hilmantel can have the exact clause that he

can find, if you're interested, while we continue the discussion.

DR. WEISS: Well, whether or not we find that, I guess the recommendation is that we have some stability as far as topography or wavefront measurements, if that's not included. And I would assume we can't have stability as far as wavefront measurements, because you usually only would get one measurement. But if there's any change in topography, that would be an issue.

Any other -- Dr. Heuer.

DR. HEUER: Having worked many years ago on an ANSI standard in a different realm, one of the components we had was certain number of anticipated potential adverse events with a forced choice of yes/no, to make sure that they're gathered in a systematic way, so that then we can - getting back to our previous discussion - we can provide patients with real numbers about how often they might expect to have this occur.

DR. WEISS: Dr. Heuer, could you repeat that again for me?

DR. HEUER: I think in the interest of providing reproducible data that patients can look at in terms of what's my likelihood of getting dry eye syndrome? What's my risk of developing an infection? What's my risk of developing epithelial ingrowth and needing flap things? If you don't have some forced choices at each key visit, does the patient have X? Yes/No? Y? Yes/No? So there are forced choices that are a much better way to collect data systematically, than just having to blank any adverse events.

DR. WEISS: Do we know how they're presently collecting the data for adverse events?

DR. EYDELMAN: The standard does not usually go into that kind of detail.

DR. HEUER: As a glaucoma specialist, we did, but that's -- all I can speak from is when we had -- in the ocular

hypertension treatment study, when we didn't specify a regimen by which events were gathered, the range from center to center in terms of how often things were reported varied extremely widely, so I think if the intention is to gather a robust data set on the real incidence of these problems, that's the only way you're going to get the information. Not seeing what's in the ANSI standard makes it a little hard to otherwise blanket accept it.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Just to address the earlier statement. The standard does say that topography should be performed on all study subjects.

DR. WEISS: Dr. Musch. If there are no other comments, then there were minimal issues with the ANSI Standard. The question was whether there could be forced choices to get some statistics on post-operative problems, such as glare, HALO, dry eyes, and also have topography included, which I think

you just mentioned it already was.

We will now go on to our final question, question four.

DR. LEPRI: "The training packet for SightNet participants currently emphasizes evaluation for and reporting of the following LASIK-related adverse events and complications: Infectious keratitis, endemic cases of diffuse lamellar keratitis, abnormal trends in post-operative topography, significant losses of best corrected visual acuity, glare, HALOs, starbursts and distortions, device failures. Please discuss any recommendations you may have for revision of this list of adverse events and complications for which reporting is emphasized."

DR. WEISS: Any comments from the panel on this last question? Dr. Heuer.

DR. HEUER: I mentioned earlier, again as a non-informed, non-corneal surgeon, but I thought epithelial ingrowth, at least

those require re-operation, ought to be enumerated.

DR. WEISS: Dr. Huang.

DR. HUANG: I think these items should be categorized into the intraoperative and post-operative. Such as intraoperative, you may have a buttonhole, you may incomplete flap, you may have a free flap, free cap. And then post-operatively you have a DLK, you have epithelial ingrowth, you have glaucoma, you have retina detachment, those kind of -- so that would be easier for people to report. And, also, that will be easier to dedicate the responsibility, because some of the post-operative finding is not really in the surgical center. It's the physician's responsibility to report, and then some of them is surgical center.

DR. WEISS: Any other comments on this question? I would question when it says "significant losses of best corrected visual acuity". Do we specify what "significant" is?

And the reason I'm asking is, we've heard from patients with adverse events today that they might have been told they had "good vision". They were 20/25, but they couldn't see anything, so it would be very good to capture those people with good visual acuity who have visually disabling problems.

DR. LEPRI: This list was, first of all, not ever intended to be limited to these events, and that is not specified what we mean by "significant losses of best corrected visual acuity", and probably would be with the limit of two lines of acuity, as is the standard in most of the labeling. Okay. Unless you have a different recommendation.

DR. WEISS: Well, I guess, perhaps what we should say is significant losses of best corrected acuity, or significant distortion in vision, because I think glare -- - the presence of glare, HALO, starburst, distortions may be there -- I think we've heard here today there are two different

animals here. We have those patients who come in the next day who are thrilled with their LASIK, and then tell you oh, by the way, I have a little bit of a HALO, and then it goes away in a couple of months, and they're very happy patients. And then we have those people who have been reporting to us today, they have visually disabling starbursts and HALO, and I think we have to start, if we are not already, distinguishing between the side effect that disappears, and the complication. Dr. Eydelman.

DR. EYDELMAN: So, if I understand the recommendation correctly, we should add an emphasis on the collection of the changes or significant impact on the quality of vision, in addition to the quantity, or the actual acuity.

DR. WEISS: Exactly. I think that's terribly important.

DR. EYDELMAN: Duly noted.

DR. WEISS: Dr. Smith.

DR. SMITH: The other thing, since you're not really -- that's not prescriptive. People can report other things. You might just remind them by saying, and any other unexpected abnormality, something like that as a prompt for people to think oh, gee, why did that happen?

DR. WEISS: Any other comments from the panel? Dr. Huang.

DR. HUANG: If I'm not mistaken, I certainly hope through this panel meeting and in this public hearing that we can clarify that this is -- FDA is approving the device, rather than censoring the procedure. And what happened is, just like auto industry, making the car super fast does not make the car industry guilty of killing people. And the same thing, the LASIK machine itself is not creating the problem. It's the procedure itself is creating the problem, so we should identify the problems related to the procedure, or related to the machine, or the

devices. And then to report it accordingly, rather than lump everything together, and everybody at the end is confused.

DR. WEISS: So to summarize the answer of the panel to question four, there's been a recommendation that when possible, intraoperative complications, such as flap complications, be distinguished from a list of post-operative complications, which would include such items such as epithelial ingrowth. And then, also, to not only include significant losses of best corrected visual acuity, but significant visual side effects, or whatever word you would use for such things as glares, HALOs, or starbursts, which could impact adversely on patient life.

I'd like to thank the members of the public who have shared with us their experiences. And I'd like you to know that we've heard your testimony, and we take it seriously. It's very hard to be a patient. We've heard very disparate reports of LASIK

from the fact that so many people are happy and their lives have been changed in such a positive fashion, to those who have spoken to us before, and have told us tragic stories, and also have told us how adversely their life was affected by visually disabling symptoms.

I guess the question is which one of this painting of the LASIK picture is true. And, obviously, for those of you who have stayed through the whole meeting, they're both true. It appears that although we don't have all the statistics we need, and the National Eye Institute, the FDA, the Academy of Ophthalmology, and ASCRS will be working to get better statistics.

Even with the statistics we have, we have information that the vast majority of patients with LASIK do very well, and are happy, and do not have visually disabling effects and see very well. However, we do -- we have heard from the FDA in their slide which said the LASIK post-market assessment

surveys do not adequately evaluate the effects of rare severity. And it appears that many of you who have had some of these adverse effects, and it may be less than one percent are in this room with us today. And that does not negate the importance of when that rare side effect happens to you, because you have to deal with it. And the FDA, and medicine, in general, want to do what can be done to help you deal with this.

Now, one other thing, which goes sort of beyond what FDA does, and it's been brought up indirectly, is listening to the many people who are testifying, there were certain commonality of things that came up. One was aggressive marketing. The other one was LASIK as a commodity.

We all know LASIK is not a commodity. It's a surgical procedure, but it is being sold as a commodity.

Are these issues that fall for the FDA? No, they don't. This is FTC. The FDA

does not regulate marketing, but I would agree with you, it is a problem.

Another thing that has come up again, more than once here, is inadequate informed consent, and the fact that some patients were poor candidates. Does that fall under the purview of the FDA? No. Some of that will fall under medical malpractice, and that's something that the field should monitor and your local malpractice lawyer is probably helping some of you with.

I think some of you came here today, and I know some of the press had touted this meeting as a referendum on LASIK. It appears to me from hearing what has been said today that this has really been a referendum on the performance of LASIK by some surgeons who should be doing a better job. And I would like, and I hope the field, in general, will help you get the answers to some of this. And I think the FDA and the organizations will help in terms of getting further information

to try to make things better for future patients, so that your testimony here has been of value, and we thank you.

We will be going on to the next session after a short break. I'd like to ask Dr. Eydelman if she has any closing comments.

DR. EYDELMAN: I just want to reiterate my personal thanks to all of you who took the time to come and tell us your personal stories. It is of value. We do hear, and we are trying to do everything in our power to try to maximize patient safety through every avenue that is under FDA's purview.

DR. WEISS: Thank you very much to those members of the public who will be leaving. You're welcome to stay. We have a 15-minute break, and then we will be going on to Phakic intraocular lenses.

(Whereupon, the foregoing matter went off the record at 3:42 p.m. and went back on the record at 3:52 p.m.)

DR. WEISS: This afternoon's session will be on phakic intraocular lens post-market experience. We will now proceed with a general discussion regarding phakic intraocular lenses.

Prior to hearing a presentation from FDA, we will hold the open public hearing session for this meeting, and we will now proceed with the open public hearing. I will repeat as I did this morning the disclosure recommendations.

Both the Food and Drug Administration, and the public believe in a transparent process for information-gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to

advise the Committee of any financial relationship that you may have with a company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first presenter is Dr. Scott Barnes, who will be presenting a statement from Dr. Doyle Stulting.

DR. BARNES: Good afternoon. I will read this in the first person, as it's written. My name is Doyle Stulting, and I'm here on behalf of the American Society of

Cataract and Refractive Surgery to comment on phakic intraocular lenses.

In addition to practicing medicine, I am a consultant for AMO, which manufactures an excimer laser and markets a phakic intraocular lens. Phakic intraocular lenses are plastic artificial lenses that are implanted into the eye to correct severe nearsightedness. They are offered to patients who are poor candidates for LASIK, typically, because the amount of nearsightedness that they have is too great to safely allow modification of the corneal curvature.

The first phakic intraocular lens was approved for use in the United States in September of 2004. This same lens has been utilized in Europe since 1991. It is a rigid plastic lens that is attached to the front surface of the iris inside the anterior chamber.

A second phakic intraocular lens was approved for use in this country in 2005.

Satisfaction with these lenses has been excellent. For example, 99 percent of patients reported during clinical trials in this country that they were satisfied with the result of the lens. About half of the patients implanted with these lenses said they could actually see better without glasses than they did before the surgery with their glasses.

I remember the first patient who received a phakic intraocular lens as part of the clinical trials in my practice. He was a firefighter who was unable to wear contact lenses successfully because of the soot and debris he encountered on the job. Just imagine the danger he faced in a burning building fighting a fire if he happened to get a piece of soot underneath his contact lens.

Patients who are candidates for phakic intraocular lenses are truly debilitated by their nearsightedness. The last patient whom I implanted was a 28 diopter

myope. I know this number may not be meaningful to all in the audience today, so allow me to illustrate my point.

I asked this patient if he could see me without his glasses. He said he could only tell if there was somebody in the room if I would actually start moving. When I asked what he would do if he were outdoors and he lost his contact lenses, he said that he would not be able to figure out where they were, and he would not be able to find his way home safely.

These devices meet a true medical need in patients who are completely debilitated without optical correction. Phakic intraocular lenses have been available for implantation outside of the United States for 17 years, and the lenses are still used by our international colleagues who have now had an opportunity to evaluate their performance over the past two decades.

These lenses are a great example of

the technology that is life-altering for patients whose safety is at risk, because they are so extremely nearsighted, yet are not appropriate candidates for LASIK. Thank you for the opportunity to address the panel."

DR. WEISS: Thank you very much. Do any members of the panel have any questions?

Hearing no questions, we will now go on to the FDA presentation. Dr. Kesia Alexander will be the first speaker.

DR. ALEXANDER: Good afternoon. My name is Kesia Alexander, and I'm the Branch Chief of the Intraocular and Corneal Implants Branch.

Today I'm going to talk briefly about FDA's safety initiatives as related to phakic IOLs, and following my presentation, Don Calogero will speak about the application ANSI and ISO standards.

At the end of our session, we would like input from the panel on ways to improve

on the following safety initiatives. During my presentation, I will discuss the following topics: approved phakic IOLs, patient labeling, and our phakic IOL website.

Currently, we have approved two pre-market applications for phakic IOLs. The first approval was for Ophtec's Artisan IOL, which is distributed here in the United States by Advanced Medical Optics under the name of Verisyse. This PMA was approved in September of 2004 to treat patients with minus five to minus 20 diopters of myopia. The second PMA is for the STAAR's Visian Implantable Collimer Lens, which was approved in December of 2005 to treat patient with minus three to minus 15 diopters of myopia. Both of these companies have post-market approval studies underway.

As part of our approval process for these types of devices, and to insure that patients are properly informed, we request that in addition to physician labeling, that sponsors provide patient labeling which gives

an overview of how the device works, risk and benefits associated with the device, alternative treatments, as well as other important aspects that the patient should consider.

We strongly encourage anyone considering these types of devices to thoroughly read the patient labeling, and to ask as many questions as needed to make an informed decision; that is, do the benefits outweigh the risks?

As you can see, I've highlighted the fourth bullet, as I would like to briefly go through some of the contraindications, warnings, and precautions associated with these types of device. Some other aspects will be discussed later in my presentation.

Phakic IOLs are contraindicated for patients who are less than 21 years of age, who have an anterior chamber depth outside of the approved range, who have an abnormal iris, who are pregnant or nursing, and who not meet

the minimum endothelial cell density requirement.

The warning section of the patient labeling highlights some of the limitations, and our knowledge of these types of devices. For example, rate of cataract formation, occurrence of lens opacification, and effects on the corneal endothelium.

In the precautions section of the patient labeling, patients are urged to thoroughly read the brochure, and to ask doctors questions. If they have any of the following conditions, they are asked to discuss with their doctor whether they are a suitable candidate. Please keep in mind that these slides are merely excerpts from the patient labeling, and that the contraindications, warnings, and precautions are based on the clinical data presented in the PMA applications.

As I mentioned in the beginning, we will be asking the panel if they have any

recommendations for improving our patient labeling.

In addition to patient labeling, we currently have a website available which addresses the following. As you can see, a few topics are highlighted in yellow. I would like to talk about these a little more to give you an idea as exactly what our website offers. However, more details regarding these areas are included in your packets. Therefore, please keep in mind that I will just be showing excerpts from these sections.

Are phakic IOLs right for you? The website advises that phakic IOLs are probably not right for a patient if the patient has large pupils, a shallow anterior chamber, low endothelial cell counts, or other risks listed on this slide. Therefore, it is very important that patients discuss the risk factors with their doctor.

What are the risks? When deciding whether the benefits outweigh the risks, our

website recommends that patients consider risks such as vision loss, retinal detachments, debilitating visual symptoms like glare and HALOs, among others, while keeping in mind that long-term data regarding these devices are not available.

The website outlines what a patient can expect before, during, and after surgery. Our website urges patients to get an initial examination to determine whether their eye is suitable for surgery, to inform their doctor of any medications they are taking, to make sure all their questions have been adequately addressed prior to signing the informed consent.

Our website provides a general overview of what the patient may expect during surgery. The website also describes what the patient should expect immediately following surgery, such as, they may be sensitive to light, and have a foreign body sensation. It also advises them when to contact their

doctor. For example, if they have severe pain. Here are some additional post-surgical expectations. You can take a few minutes and look them over.

In this slide, I'm showing you a sampling of the types of questions from our website that the patient should consider asking their doctor. Similar types of questions are also provided in patient labeling. Please keep in mind that our list of questions are not intended to be all-inclusive. The hope is that they will guide the patient in the right direction to ask questions which will specifically address their concerns.

Once again, we will be asking panel input, and asking the panel if they have any recommendations on improving our phakic IOL website. Thank you.

DR. WEISS: Thank you very much. Are there any questions for Dr. Alexander? There are no other FDA presentations.

DR. CALOGERO: Hello. My name is Don Calogero. I'm in the Division of Ophthalmic, Ear, Nose and Throat Devices.

There are currently two phakic IOL standards that are published, one is ISO 11979-10 for phakic IOLs, and the other is ANSI Z80.13. The ISO standard is currently recognized by FDA in its entirety with no additions. The ANSI standard is currently being reviewed for recognition. Any modifications that the panel recommends to these standards will be presented to the standards organizations at the time of the revision of these standards.

These standards contain both pre-clinical and clinical requirements. In terms of the pre-clinical requirements, all of the optical, mechanical, biocompatibility, sterility, shelf life, and transport stability testing for phakic IOLs are the same as the requirements for the monofocal IOLs, with the following exception.

There is a requirement for a clearance analysis. And this is an analysis of the location of the phakic IOL surface with respect to ocular tissue that must be conducted to establish the minimum anatomical dimensions acceptable for the PIOL design, and the range of powers it would be available in.

Now, in terms of the clinical requirements, the ISO PIOL standard contains suggested design of the clinical investigation that will collect the data needed to determine the safety and the performance of the PIOL. Now, in the next group of slides, what I'll do is I'll summarize some of the important elements that are described in the standard. One concerns the study design, and it recommends a non-controlled study with a minimum study duration of three years to evaluate both the maintenance of ECD, and the rate of cataract development.

Element number two is the primary endpoint, and that's endothelial cell density.

And the changes in ECD in the phakic IOL subjects are compared to the normal rate of loss. The third element is a specific exclusion criteria that's associated with these phakic lenses, and that recommends in the standard that subjects below a recommended minimum EDC by age be excluded from the study to minimize the possibility of corneal decompensation later in life.

The next element is subject enrollment, and it recommends that subjects be enrolled in three phases; Phase One, 10 subjects followed for six months; Phase Two, 100 additional subjects followed for six months; and then Phase Three are the remaining subjects. The recommended sample size is 300, and that's the minimum needed to detect clinically significant drops in ECD.

The fifth element is the recommended pre-op/post-op exams, and ISO recommends, and ANSI recommends distance UCVA, distance BSCVA, near VA with distance spectral

correction, manifest and cycloplegic refractions, axial length, ACD, intraocular pressure, slit lamp exam, status of crystalline lens, gonioscopic exam, fungus exam, mesopic pupil size, pachymetry, keratometry, subject questionnaire, and spectral microscopy.

There are two sub-studies that are required in the standards. One is a contrast sensitivity study, and that's to assess the contrast sensitivity losses that may be associated with the phakic IOL. The second sub-study is a clinical clear analysis and sub-study, and that's performed on all subjects in Phase One to determine the clearances between the phakic IOL and the ocular tissue. And this clearance study would validate the pre-clinical data that was determined.

Some key recommended safety analyses in the standard are the rate of ECD change, the rate of cataract development, and

the percentage of subjects that lose two or more lines of BSCVA.

The standards have very specific clinical labeling requirements, and they require a summary of the clinical results of the investigation, any recommendation for periodic evaluations after implantation, and any restrictions in the indications for use if necessitated by the anatomical clearance analysis, and the clinical evaluation.

Okay. Thank you. Okay. We're up to the panel questions now.

DR. WEISS: So now can I safely say there are no other FDA speakers?

DR. CALOGERO: I believe so, yes.

DR. WEISS: Okay. I know eventually I'd get it right.

Now we're going to go on to the FDA questions to the panel. We're going to start with question one.

DR. CALOGERO: Okay. Question one is, "Please discuss any recommendations you

may have for modifications to patient labeling of phakic intraocular lenses."

DR. WEISS: I'm going to ask for volunteers on this one. Does anyone want to make a comment?

I have a question. Do we indicate in the patient labeling whether astigmatism, or the effect of the wound on inducing astigmatism, or the fact that this won't correct their astigmatism?

DR. CALOGERO: Not in the standard. I don't know if in the FDA labeling for the two --

DR. WEISS: This is the patient labeling for question number one. So is it indicated in the patient labeling, the effect of this on inducing astigmatism, or not treating astigmatism? And if it's not, since this is a refractive lens, then I think it should be included.

DR. MUSCH: Well, Dr. Heuer and I are just reflecting on the fact that I don't

think we have patient labeling to look at. We have website information, and that's it.

DR. EYDELMAN: Yes. Since there are only two phakic IOLs currently on the market, rather than summarizing it as an attachment, the actual patient labeling for the two devices were provided in your folders.

DR. WEISS: Dr. Eydelman, how would you like the panel to handle this one, because, presumably, many have not read this, and so it may be hard for them to comment, if they haven't read it?

DR. EYDELMAN: Perhaps we can go to the next question, and then come back.

DR. WEISS: Okay. That's fine. So while -- if everyone has pulled this out, they can start skimming through this. We will then go on to the second question, and then come back. While everyone is pulling that out, we'll go on to the second question.

DR. CALOGERO: The second question, "Please discuss any recommendations you may

have for modifications to FDA's phakic IOL website."

DR. WEISS: The phakic IOL website, I believe, in our textbook, the white textbook is under Insert One. I guess I would ask the same question; do we say anything about astigmatism here? Do we say -- do we talk about the fact that long-term results are not known in the United States?

Dr. Huang, do you have any thoughts on this?

DR. HUANG: Yes, I have several recommendations. I thought the website is well-designed, but there are not enough illustration to educate our patient regarding the distinction between the two types of phakic IOL, the anterior chamber, as well as the posterior chamber. So maybe a simple diagram indicative of the position of the anterior chamber and posterior chamber IOL could be helpful.

And there are some other minor

considerations in the section of "Are phakic lenses for you?" And that we did not discuss the previous surgery, such as retinal detachment, or keratoconus, those kind of situations, so that might be a good place to educate our patient.

DR. WEISS: I have a question. Can you clarify what you'd be referring to as far as keratoconus or retinal detachment surgery in terms of the phakic IOL candidate?

DR. HUANG: What happens is that basically -- the question was just addressing, you have a problem with the posterior part of your eye, but it did not specify what kind of problems, so maybe a little bit confusing for the patient. Whereas, other part of the education material indicating you have uveitis, you have glaucoma, those kind of thing, but there's no specific indication about the corneal pathology. So I thought -- this is just a general recommendation.

DR. WEISS: Ms. Cofer, and then Dr.

Edrington.

MS. COFER: Yes. I'm looking on that page what are the risks, and the sentence says, "Some designs have shown that their implantation causes endothelial cells to be lost at a faster rate than normal". But my question is, isn't it all designs show a faster rate of endothelial cell loss, and not some designs?

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Well, there are only two phakic IOLs that are currently on the market, so we can only provide -- this is an overall overview of phakic lenses, and then there's specific data specific to those two IOLs in the labeling, and summary of safety and effectiveness, so those are two different distinctions. We provide data specific to a particular device in the labeling for that device, and this is a general overview of phakic IOLs.

MS. COFER: Can I follow-up on

that?

DR. WEISS: Actually, I'm going to -- would it not be fair, because there are only two approved in the United States, to say the two that have been approved in the United States show endothelial cell loss. And I don't know, that might be addressing your point, I would hope.

MS. COFER: My point is that both devices show an increased rate of endothelial cell loss, so it seems like this might be misleading to say some, because we have two, and they both show an increased rate of endothelial cell loss.

DR. WEISS: Dr. Edrington, please.

DR. EDRINGTON: Referring to what Dr. Huang said about keratoconus, they're more apt to need corneal transplants down the road, so that might be a strong recommendation, or contraindication for it.

And the other is the same point I made with LASIK, which is, again, if you're a

contact lens wearer, the issue is not the amount of time, but the stability.

DR. WEISS: Dr. McLeod.

DR. McLEOD: I wonder if you could clarify the contraindications specifically for keratoconus in terms of cornea transplant?

DR. EDRINGTON: It seems like it's a higher risk group for needing a corneal transplant down the road, if you're doing something to the endothelial cells.

DR. McLEOD: But usually the transplant would be based on topographic issues, not on endothelial cells. Say Fuchs Endothelial Dystrophy, that I would concur with.

I think for keratoconus or for Fuchs keratoconus, in fact, those are the patients that you wouldn't want to go near them with the excimer laser, and so with proper informed consent, the issue would probably be that all things being equal, with a deep anterior chamber, you actually might be

better off with the phakic IOL. But I don't think that that was actually studied in the FDA protocol, so I think it would be difficult to insert that.

DR. WEISS: Mr. Bunner.

MR. BUNNER: Just if somebody could clarify for me, what -- from a patient's perspective, what would be the indication of this type of a procedure versus LASIK for what appears to be low to high myopia?

DR. WEISS: Even though this was approved for minus 5, I don't know that many people are using this for minus 5. I think much of the ophthalmic community will use a phakic IOL if the patient is not a LASIK candidate. And why would you not be a LASIK candidate, if you had a very thin cornea, and a high, and required a highly myopic prescription, or if you had a highly myopic prescription and you were beyond the limitations of the LASIK. I believe that's more of what's the indication for phakic IOL

in the United States.

Does anyone have any comments, or any different experience? Okay. Any other comments on -- Dr. Heuer.

DR. HEUER: This may be as much a question, as a comment. The website talks about the increased risk potentially of cataract, and it says the lens may have to be removed at that time. Do we have any information about the ease with which that can be done, and should there be a cautionary note about perhaps we don't know to what extent this will complicate cataract surgery?

DR. WEISS: The website is fairly extensive. And from my recollection of the panel meeting, they boil down to two major issues, which was what's in front of the IOL, and what's behind the IOL; namely, the endothelium and the lens. And I would like if there was some way to distill this and underscore those two major risks, because my concern is those risks would sort of get --

flow out with the amount of information we have here. So if there was any way to underscore the two major issues, I think that would be good. Dr. McLeod.

DR. McLEOD: Just in response to Dr. Heuer's question. I think my understanding anecdotally is that generally speaking, the issue is less the removal of the lens than it is the accurate axial length measurements in the setting of two lenses.

DR. WEISS: Yes. So we're going to -- if we're going to go on to question one, or three, or whichever, we can summarize the answers of the panel to question two, recommendations for modifications of the FDA phakic intraocular lens website.

One is having a diagram of the two different types of IOLs that are approved in the United States. Two is indicating that for the two types that are approved in the U.S. presently, there has been documented endothelial cell loss. Three is to indicate

that not only do you want to be out of your contact lenses a certain period of time, but you want contact lens stability. Four is to indicate, I guess, specifics, instead of saying problems in the back of the eye, saying a little bit more specific, sort of retinal problems.

I don't know that we determined whether keratoconus would be a contraindication or an indication for phakic intraocular lens, and there may be some issues, if you need a cataract removed, because it may be more difficult to figure out the IOL power. But I think that's something the FDA would want to document what the issues are, if there are issues with removal of cataract if you already have a phakic intraocular lens.

Dr. Huang, is there -- Dr. Edrington.

DR. EDRINGTON: I would just like to clarify the keratoconus point. When you re

move the lens is there potential damage to the endothelium when you take it out, if you were to take it out?

DR. McLEOD: Certainly, with any intraocular procedure where you're going to have infusion, you're going to have some degree of endothelial cell loss.

DR. EDRINGTON: So the point was with keratoconus, since there was a higher possibility of needing a corneal transplant, and once the transplant was performed, you would want to take that lens out. At that time you would probably, possibly damage the endothelium?

DR. McLEOD: Oh, boy. So, are you saying that this is --

DR. EDRINGTON: I'm not saying everybody needs a transplant, no.

DR. McLEOD: Yes, but even if you're going to do a transplant, then your graft, your power of the cornea is going to change. And, typically, you're going to put

in a flatter cornea, so very probably you're going to change the refractive status of the eye. My guess is once you open the eye, took that cornea off, that lens is coming out.

DR. EDRINGTON: You take it out sometime.

DR. McLEOD: Yes.

DR. EDRINGTON: Okay.

DR. WEISS: Yes?

DR. ALEXANDER: Hi. I just wanted to back up to your question regarding astigmatism in the patient labeling, as well as the website.

The website doesn't specifically state that it's not treating astigmatism, but it does state that it's specifically for treating nearsightedness. In terms of having long-term data, it does state that long-term data is not available in the website.

For the patient labeling, I was just flipping through the STAAR patient labeling here, and it does state it is not

intended to correct any astigmatism you may have, or may not have. And that's on page 7 of 31 of the patient labeling.

DR. WEISS: Because with at least one of the IOLs there's a larger wound, and that can induce astigmatism, I would wonder if that should be included, that certain types of intraocular lenses, because of the wound that's created to insert the intraocular lens, can actually induce astigmatism. Because many of these patients, of course, are expecting to be glasses free, and they may need a secondary procedure to correct their astigmatism, if the astigmatism is induced.

DR. ALEXANDER: And the labeling also state that this will not make them independent or free of glasses.

DR. WEISS: Dr. McLeod, do you agree, or disagree?

DR. McLEOD: I think that a review of the data should actually render specific information about the vector changes in

astigmatism. It's certainly perfectly reasonable to assume that the data will probably show that there is at least a change in axis and degree of astigmatism, but I think the data review should allow specific language for the labeling.

DR. WEISS: So if the data shows from the studies, at least the IOL where you had a larger wound, that astigmatism or visually significant astigmatism did result in some patients, the website and patient labeling would benefit from the individuals who are considering this procedure having this added information.

I think we've concluded question two. We are now going to go to question three. And question three is, "Please discuss any recommendations you may have for future revisions of ANSI and ISO phakic intraocular lens standards." And this is in your insert number two in your white book.

I had a question as far as there's

a six month follow-up. Now six months is extremely short.

DR. CALOGERO: That was for the initial phase, for the Phase One on the first ten subjects. And, typically, the initial phases are -- FDA studies are six months before they can go to the second phase. And then there's a third phase, so it's a staged approach to minimize the risk in the standards.

DR. WEISS: What are the second and third phases as far as the length of time, or are they consistent with what the FDA does? I guess maybe that's my question.

DR. CALOGERO: Yes, they are consistent.

DR. WEISS: Okay.

DR. CALOGERO: The second phase also is 100 additional subjects, also followed for six months. So on the first 10 you'd be up to a year then, and the remaining subjects are enrolled, and the study duration I believe

is three years for the study.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: I just want to clarify. When we talk about phases, that does not mean that the patient follow-up is ceased at that point. What that means is that if the data to that point is acceptable, the sponsor can move on to the next phase of the study. So it's three-year follow-up is, I think, the question - the answer that you were searching for.

DR. WEISS: That's very helpful. Thank you. Dr. Musch.

DR. MUSCH: Dave Musch here. Maybe you can clarify for me, I know this idea of phasing in is now pretty frequent in the Device Branch, at least. What information do you expect to obtain from following 10 subjects for six months? To my mind, you would probably rule out any really bad implant, and then go on, assuming you don't see any signal events, to recruiting the next

100. And that would give you a little better ability to detect perhaps less onerous complications. But I know the number varies across devices, and it can be a rather -- a problem for a company to deal with, and maybe Barbara can comment on this. Because can you, for instance, only recruit 10 patients, follow them for six months, and not have any recruitment until those 10 patients are followed for six months, and then open the gate again? Go ahead.

DR. WEISS: Dr. Eydelman, and then Ms. Niksch.

DR. EYDELMAN: Okay. You are absolutely correct. In any device trial, whether it's phakic IOL or any others, phase one usually means make sure it's not a disaster, putting simplistically. So, again, for that, the kind of patient that's enrolled in Phase One will typically have very different profile than the patient that will ultimately be involved in Phase Three. So,

for example, it will be somebody with -- in whom risk benefit will still be worse considering the limited knowledge of the safety of the device at the time of implantation. And then as that -- and then it's really -- usually we do ask for the data to be submitted for us to decide whether it is safe enough to enroll additional patients. And regardless of how hard that might be to the sponsor, over the years that has proven to be an enormous asset in protecting patient safety. Since I cannot share all the failures, I can only tell you that there are more Phase One trials that do not go to Phase Two than you can imagine.

DR. WEISS: Dr. Musch, and also apologizes for macerating your name.

DR. MUSCH: Quite all right.

Just to follow-up. Is there variation in the number in that initial phase based on your perception of risk?

DR. EYDELMAN: Yes.

DR. WEISS: Any other comments? So, Dr. Huang, can you summarize what the suggestions were for this third question for ANSI? Yes, Dr. Musch.

DR. MUSCH: I'm sorry. I had one more question. I noticed for the sub-study of contrast sensitivity, the number 61 was indicated, which seemed to me a rather interesting number. Where did that come from?

DR. CALOGERO: There are statistics in the standard that attempt to determine what sample size would be necessary to detect a difference of .3 log units using assumptions, and it comes up to 61.

DR. EYDELMAN: This is Dr. Eydelman, again. Unfortunately, as I referred to earlier, it's very unfortunate in that due to the copyright privileges of the ANSI and ISO standards, we're not allowed to duplicate it, and actually mail you copies. So we can only make excerpts and summarize it in bulleted information. So to that, I

apologize, in that the discussion becomes a little awkward.

DR. WEISS: I had a question on the third page of this. The standards specifically require labeling to contain the following clinical information, a summary of the clinical results. I assume that also includes complications, such as percentage of patients who develop cataract or endothelial cell loss?

DR. CALOGERO: Exactly. It's not specific, but that's implied.

DR. WEISS: Okay. Dr. Huang, do you have what -- yes, please.

DR. HUANG: Well, my comment is specifically related to the FDA question, if there's any recommendation the ISO criteria. And in terms of the following pre-operative and post-operative examination, I recommend it. I think now is the anterior segment imaging, that we should consider including in either the OCT or the other anterior segment,

also high-speed ultrasound.

DR. CALOGERO: That's recommended in the Phase One to confirm the theoretical clearance analysis, so they are recommending that you do it on the first 10 subjects.

DR. HUANG: But is not recommended in the subsequent follow-up?

DR. CALOGERO: That is correct, yes.

DR. HUANG: And the other thing is the safety analysis. Appears to me that intraocular pressure or glaucoma essentially was overlooked. I don't know if this was -- at least it's not in the ISO criteria. I know in the patient education material, and the patient labeling has that, but the ISO criteria did not include glaucoma assessment, so that's my specific recommendation.

DR. CALOGERO: In terms of the analysis, I'm sorry, it is in there. I just sort of highlighted the main analyses.

DR. HUANG: Okay.

DR. CALOGERO: They have like a list of 20 or 30 analyses that they recommend, but we couldn't list them all.

DR. HUANG: Sorry. Again, we are deferring to the expert.

DR. HEUER: I'm going to make a comment about the process. If it is important for ISO and/or ANSI that the FDA adopt their standards, it would seem that they would be willing to give you permission to distribute the standards to the Committee. Asking us to make recommendations based on abstraction does not seem to be the best process.

DR. EYDELMAN: Duly noted.

DR. CALOGERO: Yes. Actually, we can do that prior to the publication of the standard. It's just unfortunate that both of these standards now have been published. If this had been say two years ago --

DR. HEUER: Even published material, you can receive copyright waivers or permission to distribute. I mean for a group

of this size, the commercial impact has to be zip.

DR. WEISS: It is what it is for this meeting.

DR. HEUER: And I'm making the point for future meetings.

DR. WEISS: For future meetings, I think you have been heard.

I think the conclusion of this discussion on question three was not any additions that I heard. Am I -- seeing that no one disagrees, we will then go on to question number four.

DR. CALOGERO: "The training manual for SightNet participants currently emphasizes evaluation for and reporting of the following PIOL-related adverse events and complications; toxic anterior segment syndrome, endophtalmitis, explant, significant ECD losses, corneal decompensation, significant losses of best corrected visual acuity. The next slide. Retinal detachments, IOP spikes,

elevations, cataract digenesis, device extrusions, device failures, damage.

Please discuss any recommendations you may have for revisions of this list of adverse events and complications for which reporting is emphasized."

DR. WEISS: Anyone from the panel have any thoughts on this list? So if I don't go around and ask people individually, would people concur that this list is sufficient as it stands? Dr. Huang?

DR. HUANG: I would like to defer this comment to Dr. Heuer. Regarding the iris atrophy, because this is significantly involving the iris manipulation, it is in one type, and in the other type requiring to put behind the iris, and so potentially will have iris chafing. So would that be -- iris atrophy should be included in the post-operative complications.

DR. WEISS: Dr. Heuer?

DR. HEUER: Well, I think in terms

of it being a risk, it's probably more of a risk if, in the long term, there's continued shedding. And I'm not sure, short of transillumination photographs and a reading center how you would quantify that. I assume that perhaps the intraocular pressure would be the surrogate, at least in terms -- it's not a perfect surrogate, because the meshwork can clear a fair amount of pigment, but that's how I would do it. I think it would be very difficult to try and quantify that.

DR. WEISS: For any members of the panel, would it be helpful to include uveitis to this, or that would not be relevant?

DR. SMITH: This is Dr. Smith. That's what I was going to add.

DR. WEISS: Okay.

DR. SMITH: I think it should be added.

DR. WEISS: Uveitis is a suggestion. Any other thoughts?

I have a question on, again,

significant endothelial cell density. That could be subject to interpretation, and if you had a 25-year old who lost, let's say, 100 cells in six months, or 200 cells, and 200 later, maybe it's not, by itself, significant, but maybe the trend is significant. So how do you quantify that a little bit so everyone is on the same page? And I don't know if you can.

DR. EYDELMAN: Perhaps Mr. Calogero can address how -- what's done for endothelial cell grid in the phakic IOLs. And I think that will help elucidate the question.

DR. CALOGERO: Well, I guess this is actually geared towards the individual patient, rather than a study. In terms of the study, usually you can detect 1.7 percent difference between the two groups, so that's considered clinically or statistically significant.

For an individual patient, you're right. You have to take into account the

variation, the repeatability of the measurement, the differences between one piece of equipment, one spectral microscope and another spectral microscope, so it's going to have to be somewhat higher than this 1.7 percent.

Off the top of my head, I don't really have any clear-cut guidance as to what would trigger this, but it's certainly something that hopefully we can clarify.

DR. WEISS: Yes. I would think that would be really important to clarify, since the endothelial cell loss is something that is a major long-term question, and you would want people to be triggered to report this sooner, rather than later.

Dr. Huang, and then Dr. Musch.

DR. HUANG: Referring back to the last question, I remember this was one panel meeting, and we invited Dr. Edenhauser here presenting endothelial density evaluation. And I think there was a consensus that if we

used the standard cohort, two standard deviation away from the standard cohort, that's considered significant loss. But I don't know if FDA has adopted that criteria or not.

DR. WEISS: Dr. Eydelhauser.

(Laughter.)

DR. WEISS: Long day for Dr. Weiss. Dr. Eydelman.

DR. EYDELMAN: Just to reiterate what Mr. Calogero said. You're absolutely right that we do have criteria for endothelial cell assessment for the studies. When you look at the individual patient, that criteria varies due to the variability of an individual. And then you, once again, have to make sure that the same instrument was used pre-op and post-op, that the same actual technician - sometimes there's an inter-technician variability, so there are a lot of things that we control very, very closely during our pre-market studies that do not,

necessarily, parallel in the real world, in other words, once the patient goes out there. So we will take the Committee's recommendation, go back and using -- we have a lot of data on endothelial cell loss, and various ways of analyzing it. We have extensive expertise, so we will utilize what we know to come up with a better definition for the SightNet. Thank you.

DR. WEISS: Dr. Musch.

DR. MUSCH: Just a suggestion. You have, obviously, put in some thought about age-related minimum standards for going into the surgery, and you probably projected to a certain base level, whether it's 500 cells per square millimeter, or whatever that you want left when the person dies, you could use that then to figure out by age category how much cell loss you would permit before concern is raised.

DR. WEISS: So summarizing the answers of the panel to question four,

recommendations for SightNet would be listing -- adding uveitis, and also having some more quantification, or specifics about what is meant by "significant endothelial cell loss."

Any other comments on this? If not, then I would ask for your recommendation for the question number one. Obviously, the panel members have not read this, and there are 21 pages here, so do you want us to flip through this as we sit here. If we take a 5-minute break, we may lose most, if not all of the audience, perhaps some of the panel members, too. So how would you like to have me proceed, Dr. Eydelman?

DR. EYDELMAN: Well, it is to the discretion of the Chair. However, we can either take the time for the panel members to flip through it, or we can take your recommendations towards the website, and adapt them for the patient labeling.

DR. WEISS: I would probably go with the latter, unless anyone on the panel

had anything in addition that they know they want to have in the labeling. I would say that it would be good, again, to underscore that cataracts and endothelial cell loss are a main concern. Although these other things can happen, this is a major concern, as far as what the future holds. That particularly for the one -- the lens that we're looking for to go back and see if patients had inducement of astigmatism from the corneal wound. And if they did, then people should know up front that they may have induced astigmatism. Plus, all of the other comments that were made for the website.

Does anyone have any other -- yes, Ms. Cofer.

MS. COFER: Yes. I'm looking at one of the patient labeling booklets, and I was looking for information about endothelial cell loss. And the only statement I found was the long-term effects on the corneal endothelium have not been established, which, to me, is

not communicating to a patient that it's been proven that endothelial cells are lost at a higher rate for long-term after implanation of phakic IOL. It just seems like very weak wording in the labeling, and it should be more of a warning that this does happen, and we don't know at what point. It hasn't been established to be safe at any point in time.

DR. WEISS: Well, it has -- it got approved because it was established to be reasonably safe and efficacious.

MS. COFER: At the time of the clinical trial. Is that correct?

DR. WEISS: Well, it would not be available in the United States if it did not get approved, and you get approved by being reasonably safe and efficacious. But your point of a concern on the endothelial cell loss mirrors what I was just saying, is that because this was a tie vote, and the tie was broken by the Chair, and I happened to be the Chair at that meeting, the endothelial cell

loss was a concern of panel members, and so I agree with you, for the patient information brochure, that should be underscored.

Dr. Eydelman.

DR. EYDELMAN: If I can just add. As was presented by Dr. Alexander earlier today, both of the currently approved phakic IOLs do have ongoing post-market studies. Both of them are collecting long-term endothelial cell data, so the labeling is actually current -- reflects our current knowledge. We can only state on the data that was collected. And while we're certainly going to take the panel's recommendation and try to clarify what we do know, at this point, there is no long-term data, per se.

DR. WEISS: Any other thoughts on this? Yes? One more. Yes.

MS. COFER: I had a separate question. In the labeling, it says the effect of pupil size on visual symptoms is not known, but I thought I saw that the visual symptoms

were worse with increasing pupil size. Was that the case?

DR. WEISS: I can't say I recall. I assume, but the FDA, I'm sure, will be willing to go back and double-check this. I assume if it made it to the patient information brochure, that was, indeed, the case in terms of proven statistically. But if there was any deviation, then I'm sure they would be willing to revisit this issue.

Any other -- Dr. Heuer.

DR. HEUER: In my flipping through, I found a couple of typos, or editorial things, I can just give it to Karen after the meeting, rather than take the time.

DR. WEISS: Would you prefer it be done that way?

DR. EYDELMAN: Yes.

DR. WEISS: Okay. So after the meeting, Dr. Heuer will do his spell-check. And if there are no other comments, then basically for the patient labeling, depending

on what the original study did, indeed, show, we will have comments on the astigmatism, comments on endothelial cell loss, or underscoring it, and pupil, if there was any issue with pupil, it will be included. As well as including those recommendations that the panel has made for the website.

We have finished all four questions, Dr. Eydelman. And are there any other announcements, or any other issues that you want the panel to address?

DR. EYDELMAN: Just wanted to thank the panel and the Chair for sticking to the tight time frame, and getting us through the day before 5 p.m.

DR. WEISS: Always do it.

I want to thank the FDA. I want to thank the members of the panel, and thank the audience, and good travels. Meeting adjourned.

(Whereupon, the proceedings went off the record at 4:48:05 p.m.)

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